ATXN1 and *ATXN2* intermediate expansions in non-SCA neurodegenerative disorders

ePoster #
EP11.084

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Abstract Spinocerebellar ataxia 1 (SCA1) and 2 (SCA2) are a group of rare, neurodegenerative disorders caused by abnormally expanded CAG repeats in *ATXN1* and *ATXN2,* respectively (normal ranges for *ATXN1* and *ATXN2* are 6-32 and 13-31, respectively). CAG expansions of >38 repeats in *ATXN1* cause SCA1. Alleles with >33 CAG repeats in *ATXN2* cause SCA2. Interestingly, intermediate alleles, not associated with SCAs, have recurrently been described as risk factors or modulators for other neurodegenerative diseases, but consensus about their role still awaits. **Material/Methods:** Whole genome was sequenced using Illumina Novaseq 6000 from prefrontal cortex of 150 brain donors without previous genetic testing, but clinically and anatomopathologically diagnosed for various neurodegenerative disorders, none of which was SCA. Incidental findings of *ATXN1* and *ATXN2* expansions were analysed using *Stripy.* Results were validated by PCR and TP-PCR using the Imegen® SCAs Kit. **Results:** We identified 16 and 17 patients of various neurodegenerative disorders with intermediate expansions (IE) in *ATXN1* and *ATXN2*, respectively. Two of them showed IE for both genes. Our data further supports a role for IE in *ATXN1* and *ATXN2* as risk factors for various non-SCA, neurodegenerative disorders. Further, preliminary results may point towards an earlier disease onset in patients with IE. **Conclusion:** IE in *ATXN1* and/or *ATXN2* may be relevant predisposing factors for several non-SCA neurodegenerative disorders, therefore genetic testing shall be considered for more accurate diagnosis and genetic counselling in some cases. It is worth reiterating that this series of patients had anatomopathologically-confirmed diagnoses, which is typically missing in previous studies.

Keywords: *ATXN1*, *ATXN2*, intermediate CAG expansion, neurodegenerative disorders, neurodegeneration.

Introduction

Spinocerebellar ataxia 1 (SCA1) and 2 (SCA2) are polyglutamine disorders; a group of rare, autosomal-dominant inherited, neurodegenerative disorders caused by an abnormally expanded cytosine-adenine-guanine (CAG) repeats in *ATXN1* (>39 repeats) and *ATXN2* (>33 repeats). Interestingly, intermediate expansions of *ATXN1* (33 to 38 repeats) and *ATXN2* (27 to 33 repeats) have been associated to patients with neurological disorders other than SCA, such as amyotrophic lateral sclerosis, frontotemporal dementia, Parkinson´s disease, Alzheimer's disease and others. The effect of these genotypes on the patient´s phenotype and disease progression remains unclear. Further, it is also unclear why size cut-off varies among studies, but it seems reasonable to think that cut-offs will be slightly different for different cohorts, as previously described.

Results

In a group of 150 brain donors, we found IE in *ATXN1* and *ATXN2* in 9.3% (n = 14) and 10% (n = 15) of the patients, respectively. In addition, co-occurrence of *ATXN1* and *ATXN2* IE was detected in two donors (1.3%). The remaining 119 donors (79.3%) did not show expansions in these genes. Thus, we identified either *ATXN1* and/or *ATXN2* IE in ~20% of the donors. Demographics in Table 1.

Table 1. Age of onset, age at donation and duration of the disease of donors with and without IE in *ATXN1* and/or *ATXN2*. Units are expressed in year (years old ± SD).

	Age of onset	*Age at donation*	*Disease duration*
ATXN1	69.3 ± 13.0	79.9 ± 11.1	10.6 ± 7.8
ATXN1/ATXN2	68.5 ± 4.9	77.0 ± 11.3	8.5 ± 6.4
ATXN2	71.1 ± 10.7	78.6 ± 12.3	7.5 ± 5.1
w/o expansion	68.7 ± 9.1	77.0 ± 9.6	8.3 ± 5.3
Total general	**69.0 ± 9.6**	**77.4 ± 10.0**	**8.4 ± 5.6**

We had selected cases of 15 neurodegenerative disorders and found IE in *ATXN1* or *ATXN2* for nine of them, namely amyotrophic lateral sclerosis (ALS), Alzheimer, corticobasal degeneration, frontotemporal dementia (FTD), FTD + ALS, mixed dementia (MD), multiple system atrophy (MSA), Parkinson and progressive supranuclear palsy (PSP). ALS (n = 20), Alzheimer (n = 55), PSP (n = 30) and Parkinson (n = 18) were the most frequent disorders. Within these disorders, 30% (ALS), 20% (Alzheimer), 10% (PSP) and 11% (Parkinson) of patients carried an IE of *ATXN1* and/or *ATXN2 (Table 2)*. These proportions are comparable with some previous studies, but differ from others.

Table 2. Frequency and percentage of cases with and without IE in *ATXN1* and *ATXN2*. ALS, Amyotrophic lateral sclerosis; Cort Deg, Corticobasal degeneration; FTDL, Frontotemporal lobar dementia; MD, Mixed dementia; MSA, Multisystem atrophy; PSP, Progressive supranuclear Palsy. Blank spaces denote absence; NA is for a diagnosis still to be decided.

	Expanded gene				
Disease	***ATXN1***	***ATXN1/ATXN2***	***ATXN2***	**w/o expansion**	**Total general**
ALS	2 (10%)	1 (5%)	3 (15%)	14 (70%)	**20**
Alzheimer	6 (11%)		5(9%)	44 (80%)	**55**
Amyloid Angiopathy				1 (100%)	**1**
Astrogliopathy				1 (100%)	**1**
Cort Deg			1 (33%)	2 (67%)	**3**
FTD	2 (50%)	1 (25%)		1 (25%)	**4**
FTD + ALS			1 (50%)	1 (50%)	**2**
Lewy				1 (100%)	**1**
MD	1 (100%)				**1**
Mitocondriopathy				1 (100%)	**1**
MSA	1 (11%)		2 (22%)	6 (67%)	**9**
Parkinson	2 (11%)			16 (89%)	**18**
Pick				2 (100%)	**2**
PSP			3 (10%)	27 (90%)	**30**
Brain vascular failure				1 (100%)	**1**
NA				1 (100%)	**1**
Total general	**14** (9.3%)	**2** (1.3%)	**15** (10.0%)	**119** (79.3%)	**150**

In patients with IE in *ATXN1*, CAG expansion size ranged 29-36 repeats. Likewise, in patients with IE in ATXN2, CAG expansion size ranged 20-33 repeats. IE found in *ATXN1* and *ATXN2* ranged 33-36 and 27-33, respectively. All patients were heterozygous, with small allele sizes of 29-31 in *ATXN1* and 20-27 in *ATXN2*. Case 2 had both *ATXN2* alleles in the intermediate range (27-33). Interestingly, in Case 1 and Case 28, we found IE in both *ATXN1* and *ATXN2*. Surprisingly, the most frequent alleles were 35 and 27 repeats for *ATXN1* and *ATXN2*, respectively (Figure 1).

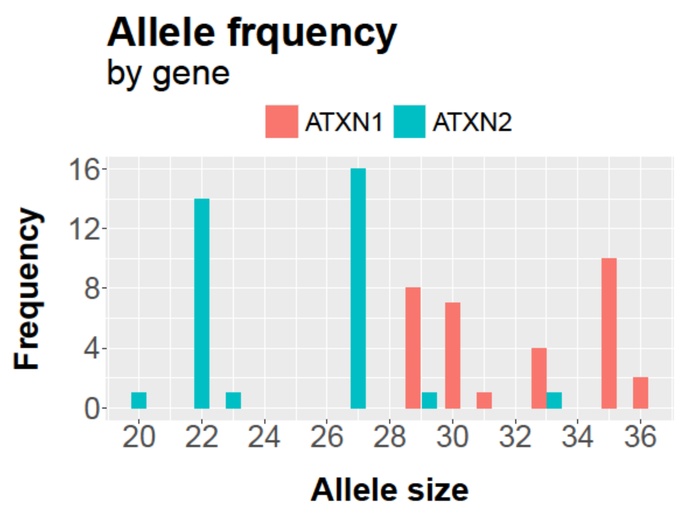

Figure 1. Allele frequencies for the cases with IE in *ATXN1* and *ATXN2*.

Preliminary analyses revealed that patients with IE showed a 2.3 years earlier disease onset than those without expansion (-4.60 to -0.05; p = 0.023). Specifically, patients with IE in *ATXN1* developed symptoms 3.5 years earlier than those without IE (-6.59 to -0.56, p = 0.010), while patients with IE in *ATXN2* developed their symptoms 1.1 years earlier than those without IE, although this difference was not significant (-4.09 to 1.89, p = 0.236). Interestingly, Alzheimer patients with IE in *ATXN1* showed a significantly earlier disease onset (-4.8 years; -9.11 to -0.53, p = 0.028). These results may indicate associations and trends between the presence of *ATXN1* and *ATXN2* IE and age of onset in patients with neurodegenerative diseases. We acknowledge important limitations, so further research is needed to confirm these findings.

Conclusions

Genetic risk factors show variability among populations, so it is key to characterise local populations. Despite having small effects on the phenotype, they might be important. Therefore, IE in *ATXN1* and *ATXN2* should be considered for further research and for genetic counselling due to their possible role as risk factors for neurodegenerative disorders. Our data further supports previous studies showing that IE of these genes play a role in non-SCA patients and previous evidence showing that these genetic variants may be important risk / predisposing / modulatory factors in several neurodegenerative disorders. We further emphasise the need for local studies to precisely characterise local populations.

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