Poster P10.049.A

Repeat expansions in *HTT* and *ATXN2* and the risk of ALS in a Norwegian cohort

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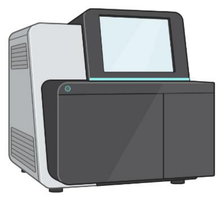
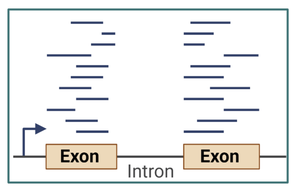
Introduction

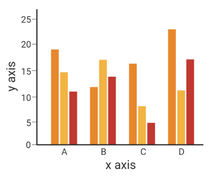
- ✓ Genetic repeat expansions may cause multiple clinical phenotypes and play a role in several neurodegenerative diseases.
- ✓ *HTT* repeat expansions have been reported in individuals with ALS.
- ✓ *ATXN1* and *ATXN2* repeat expansions (≥ 33 repeats and ≥ 29 repeats) are known genetic risk factors of ALS.
- ✓ *AR* repeat expansions cause Kennedy's disease; a differential diagnosis of ALS.
- ✓ ExpansionHunter software detects repeat expansions on exome sequencing data.

Methods

ALS patients (*n* = 414) and neurologically-healthy controls (*n* = 713) → **Exome sequencing (PCR-analysis for confirmation)** → **ExpansionHunter software on exome sequencing data** → **Statistical analyses of repeat expansions in ALS patient compared to controls**







Results: Repeat expansions

HTT (36-40 repeats)

- ✓ Six ALS patients (1.5%)
- ✓ Two controls (0.3%)
- ▪ **Odds ratio 10.4*** (95% CI: 1.9-58.6)

ATXN2 (29-34 repeats)

- ✓ Seven ALS patients (1.7%)
- ✓ Three controls (0.4%)
- ▪ **Odds ratio 4.8*** (95% CI: 1.1-21.2)

AR

- ✓ One ALS patients
- ✓ None controls

ATXN1 (34-45 repeats)

- ✓ 32 ALS patients (7.7%)
- ✓ 56 controls (7.9%)
- ▪ Odds ratio 1.1 (95% CI: 0.7-1.9)

P < 0.05

Results: *HTT*

Table 1 Clinical characteristics for ALS patients carrying intermediate expansion in *HTT* gene (≥36 repeats).

	HTT+ (*n*=6) (1.45%)	HTT- (*n*=408) (98.55%)	*P*-value
Mean age at onset, years (SD)	49.00 (18.95)	63.26 (12.12)	**0.005***
Motor neuron loss, *n* (%)			
UMN	0 (0)	26 (6.37)	0.696
LMN	1 (16.67)	29 (7.11)	
Both	5 (83.33)	335 (82.11)	
Uncertain[a]	0 (0)	18 (4.41)	
Site of onset, *n* (%)			
Spinal	6 (100)	251 (61.52)	0.324
Bulbar	0 (0)	106 (25.98)	
Both	0 (0)	48 (11.76)	
Uncertain[a]	0 (0)	3 (0.74)	
Cognitive impairment, *n* (%)			
Yes	1 (16.67)	30 (7.35)	0.540
No	5 (83.33)	359 (87.99)	
Uncertain[a]	0(0)	19 (4.66)	
El Escorial, *n* (%)			
Yes	5 (83.33)	307 (75.25)	0.621
No	0 (0)	56 (13.73)	
Uncertain[a]	1 (16.67)	45 (11.03)	

[a]Includes uncertain and missing data
*$P < 0.05$.
UMN = Upper motor neuron
LMN = Lower motor neuron

Results: Allele size

Table 2 Patients with repeat expansions in *AR, ATXN2* and *HTT* with clinical characteristics.

Case ID	Gene expansion	Repeat size	Other genetic variants	Sex	Age at onset	Family with ALS	Site of onset	Cognitive involvement	Motor neuron loss	Neurophysiology compatible with ALS	El Escorial criteria fulfilled	Disease duration[a] (months)
1	*HTT*	40		M	58	No	Spinal	Yes		Yes	Yes	120
2[b]	*HTT*	39		M	32	No	Spinal	No		Yes	Yes	76*
3	*HTT*	39	*C9orf72* expansion	F	69	No	Spinal	No		Yes	Yes	10
4	*HTT*	39		M	70	No	Spinal	No		Yes	Yes	49
5	*HTT*	36	*SOD1*[c]	M	28	Yes	Spinal	No		Yes	Uncertain	116*
6	*HTT* *ATXN2*	37 31	*C9orf72*[d]	M	37	No	Spinal	No		Yes	Yes	157*
7	*ATXN2*	34		M	55	No	Spinal	No		Yes	Yes	85
8[e]	*ATXN2*	33		F	64	No	Spinal	No		No	No	145*
9	*ATXN2*	30		M	71	No	Spinal	No		Yes	Yes	11*
10	*ATXN2*	30		M	77	No	Spinal	No		Yes	Yes	19
11	*ATXN2*	29		F	67	No	Spinal	No		Yes	Yes	34
12	*ATXN2*	29		F	61	No	Bulbar	No		Yes	Yes	32
13	*AR*	45		M	67	No	Both	Yes		Yes	Yes	32*

[a]Defined by months from symptom onset
[b]Family history of Huntington's disease
[c]p.(His47Arg)
[d]Intermediate repeat expansion (27 repeats)
[e]Diagnosed with primary lateral sclerosis
*Not deceased

- ✓ Medical records were re-evaluated by two independent neurologists.

Results: Clinical characteristics

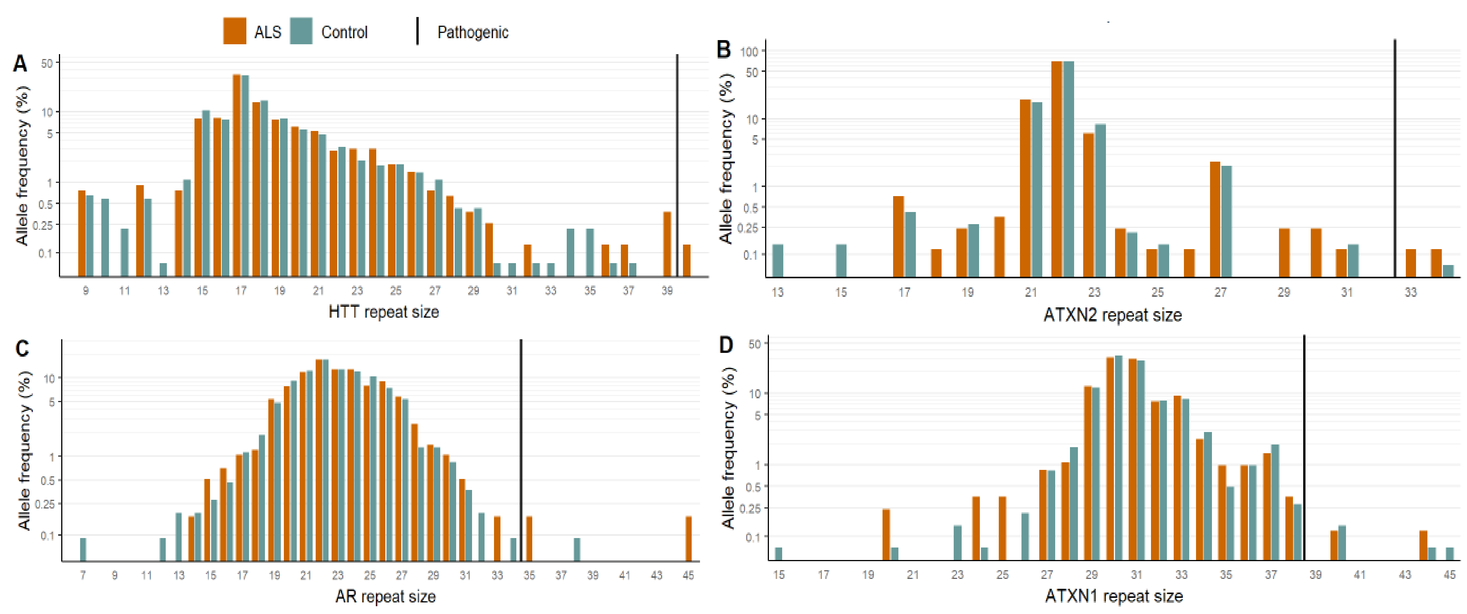


Figure 1 Distribution of total alleles and sizes in ALS patients compared to controls. (A) *HTT* repeat expansions in 391 ALS patients and 695 controls. **(B)** *ATXN2* repeat expansions in 414 ALS patients and 712 controls. **(C)** *AR* repeat expansions in 414 ALS patients and 712 controls and **(D)** *ATXN1* repeat expansions in 414 ALS patients and 713 controls. The number of ALS patients and controls differs since samples with low coverage for a specific repeat were removed from the analysis

Conclusion

- ✓ *HTT* and *ATXN2* repeat expansions is associated with increased risk of ALS in our cohort
- ✓ *HTT* repeat expansions is associated with earlier onset of ALS in our cohort

HELSE SØR-ØST

ALS Norge® Etablert februar 2008

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The authors declare no conflicts of interest

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