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

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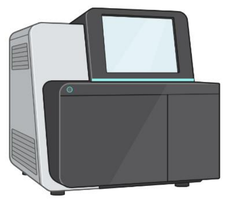
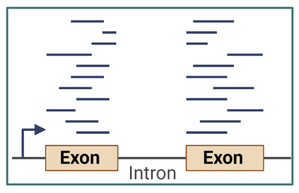
Introduction

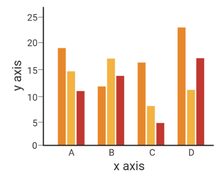
- ✓ Genetic repeat expansions can cause multiple clinical phenotypes and play a role in several neurodegenerative diseases.
- ✓ *HTT* repeat expansions have been reported in individuals with ALS.
- ✓ *ATXN1* and *ATXN2* repeat expansions (≥ 33 repeats and ≥ 29 repeats) are known genetic risk factors 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 patient
- ✓ None controls

ATXN1 (33-45 repeats)

- ✓ 50 ALS patients (12.1%)
- ✓ 96 controls (13.5%)
- ▪ Odds ratio 0.9 (95% CI: 0.6-1.4)

P < 0.05

Results: Clinical characteristics

Table 1: Clinical characteristics of patients with repeat expansions in *AR*, *ATXN2* and *HTT*.

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

[a]Defined by months from symptom onset
[b]Not deceased
[c]p.His47Arg
[d]Intermediate repeat expansion (27 repeats)
[e]Diagnosed with primary lateral sclerosis
Abbreviations: F = Female, M = Male, UMN = Upper motor neuron, LMN = Lower motor neuron

- ✓ Medical records were re-evaluated independently by two neurologists. The ALS diagnosis was confirmed in all patients with repeat expansions in *HTT* and *ATXN2*.

Results: Allele size

Figure 3 Distribution of allele frequency and allele sizes in ALS patients and 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. The dashed black line represents the thresholds of which the number of repeats are considered to be associated with ALS risk, and the black line represent the thresholds of which the number of repeats is considered to be pathogenic for each locus

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

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The authors declare no conflicts of interest