Movement disorders associated with expansions in the *C9orf72* gene

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Background and objective

Hexanucleotide repeat expansions (HRE) in *C9orf72* are a major cause of frontotemporal dementia (FTD) and amyotrophic lateral sclerosis (ALS).[1] Soon after the discovery of the gene HRE in *C9orf72* have been found to be present in multiple movement disorders (MD).[2,3]

Our objective was to define the movement disorders (MD) in patients with HRE and compare the characteristics of the *C9orf72* patients with and without MD.

Methods

We investigated 501 patients tested for HRE in *C9orf72* at the National Hospital for Neurology and Neurosurgery in London, UK between May 2012 and May 2019. A minimal size of 30 GGGGCC repeats was defined as pathogenic.[3]

Results

40 subjects had the HRE and available clinical data. **17/40 patients with HRE had MD.**

Median age at onset of symptoms was 58 years (range 8-70). In 6/17 patients MD were the first symptom and in 2/17 it was the sole manifestation of the mutation. The most common MD were **parkinsonism especially symmetric** and **postural tremor**, each one present in 11/17 subjects. Distal, stimulus-sensitive **myoclonus** in the upper limbs was present in 6/17 and **cervical dystonia** in 5/17. 4/17 subjects presented **chorea** and 4/17 had orofacial dyskinesias.

Four patients had isolated MD. The most frequent **combination** was **tremor and parkinsonism** in 8/17 patients with 5/8 presenting **also myoclonus.**
Patients without MD had significantly shorter follow up times and higher proportion of ALS.

Patient	AAO (y)	AAO MD (y)	FTD	ALS	TREMOR	MYOCLONUS	PARKINSONISM	ATAXIA	DYSTONIA	CHOREA	OROFACIAL DYSKINESIAS
1	64	64	+	-	+	-	+	+	+	-	-
2	70	70	-	+	+	+	+	-	-	-	-
3	60	60	+	-	-	+	-	-	-	-	+
4	58	58	+	-	+	+	+	-	-	-	-
5	8	18	-	-	-	+	-	-	+	+	+
6	53	56	+	-	+	-	+	-	-	-	-
7	54	61	+	-	+	-	-	-	+	-	-
8	39	50	+	+	+	+	+	-	-	-	-
9	59	69	+	+	+	-	-	-	-	-	-
10	55	55	+	-	-	-	+	-	-	-	-
11	58	58	-	+	+	-	+	-	+	+	+
12	69	72	+	-	-	-	+	-	-	-	-
13	40	40	+	-	+	-	+	-	+	-	-
14	19	19	-	-	-	-	-	-	-	+	-
15	36	41	+	+	+	+	+	-	+	-	-
16	62	66	+	-	+	+	+	-	-	-	-
17	60	61	+	-	-	-	-	-	+	+	+
TOTAL (n, % positive)			13 (76.47%)	5 (29.4%)	11 (64.7%)	7 (41.17%)	11 (64.71%)	1 (5.8%)	7 (41.12%)	4 (23.53%)	4 (23.53%)
AAO of MD mean (sd)					57.55 (10.26)	51.86 (17.80)	57.27 (10.60)	64	49 (16.83)	39 (23.7)	49 (20.87)

Conclusion

MD in patients with *C9orf72* expansions are frequent and show a distinct clinical phenotype with essential-tremor syndrome, parkinsonism, cervical dystonia, orofacial dyskinesias and myoclonus. MD frequently appear in combination and may precede signs of ALS or FTD. Shorter follow up periods due to higher prevalence of ALS might explain the absence of MD in the C9-MD-negative group.

References
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