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	MYOCYONS	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	+ - - - - - + + + + + + +

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<thead>
<tr>
<th>TOTAL (n, % positive)</th>
<th>AAO of MD mean (sd)</th>
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<tbody>
<tr>
<td>13 (76.47%) 5 (29.4%)</td>
<td>57.55 (10.26)</td>
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<td>11 (64.7%) 7 (41.17%)</td>
<td>51.86 (17.80)</td>
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<tr>
<td>11 (64.7%) 7 (41.12%)</td>
<td>57.27 (10.60)</td>
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<tr>
<td>1 (5.8%) 4 (23.53%)</td>
<td>64</td>
</tr>
<tr>
<td>4 (23.53%) 4 (23.53%)</td>
<td>49 (16.83)</td>
</tr>
<tr>
<td>39 (23.7%) 49 (20.87)</td>
<td>39</td>
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References
1Renton AE et al., A hexanucleotide repeat expansion in C9ORF72 is the cause of chromosome 9p21-linked ALS-FTD. Neuron 2011; 72:257-68
2Hensman DJ, et al, C9orf72 expansions are the most common genetic cause of Huntington disease phenocopies. Neurology 2014; 82:293-9

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