C9orf72 hexanucleotide repeat length in older population: normal variation and effects on cognition

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A B S T R A C T

The hexanucleotide repeat expansion in C9orf72 is a common cause of amyotrophic lateral sclerosis/fron-totemporal dementia and also rarely found in other psychiatric and neurodegenerative conditions. Alleles with >30 repeats are often considered an expansion, but the pathogenic repeat length threshold is still unclear. It is also unclear whether intermediate repeat length alleles (often defined either as 7–30 or 20–30 repeats) have clinically significant effects. We determined the C9orf72 repeat length distribution in 3142 older Finns (aged 60–104 years). The longest nonexpanded allele was 45 repeats. We found 7–45 repeats in 1036/3142 (33%) individuals, 20–45 repeats in 56/3142 (1.8%), 30–45 repeats in 12/3142 (0.38%), and expansion (>45 repeats) in 6/3142 (0.19%). There was no apparent clustering of neurodegenerative or psychiatric diseases in individuals with 30–45 repeats indicating that 30–45 repeats are not pathogenic. None of the 6 expansion carriers had a diagnosis of amyotrophic lateral sclerosis/fron-totemporal dementia but 4 had a diagnosis of a neurodegenerative or psychiatric disease. Intermediate length alleles (categorized as 7–45 and 20–45 repeats) did not associate with Alzheimer’s disease or cognitive impairment.

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1. Introduction

C9orf72 hexanucleotide repeat expansion is a major cause of sporadic and familial amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD) (DeJesus-Hernandez et al., 2011; Renton et al., 2011), and it is particularly common in Finland (Majounie et al., 2012). Expansions can span up to several 1000 repeats, but the minimum length of pathogenic expansion is not known. Knowledge on the distribution of repeat lengths in the general population could help gain a better understanding of the threshold for pathogenicity. Perhaps the most widely used threshold for expansion is 30, defined in one of the original studies describing the C9orf72 repeat (Renton et al., 2011). Determining a threshold for expansion is complicated by the difficulty of reliably determining repeat lengths, and thresholds reflect more the limitation of used methods than actual alteration in biologic function. Southern blot is considered to be the gold standard of repeat length estimation but because of its high demand of good quality DNA, cost, and work load, often other methods such as repeat-primed PCR (RP-PCR) are used.

Besides genuine expansions, “intermediate length” alleles (defined often as 7–30 or 20–30 repeats) have also been hypothesized to...
predispose to neurodegenerative diseases. In luciferase reporter assay, intermediate alleles showed decreased C9orf72 promoter activity as compared to short repeat alleles (Gijselinck et al., 2016). Moreover, adverse effects have been observed in a fly model with 30 repeats (Zhang et al., 2015), although the relevance of fly physiology to human pathophysiology in this context is unsure. As with expansion, the threshold for intermediate length repeats also varies in studies but allele length ≥7 has been shown to associate with the C9orf72 founder haplotype in the European population (van der Zee et al., 2013). A recent review (Ng and Tan, 2017) summarized that most studies do not find association between intermediate length alleles and a variety of neurodegenerative diseases but intermediate length alleles might be associated with psychiatric symptoms. Most studies on intermediate length alleles focus on ALS/FTD spectrum but only few on Alzheimer’s disease (AD) (Cacace et al., 2013; Harms et al., 2013; Jiao et al., 2013; Kohli et al., 2013; Xi et al., 2012).

In this study, we present C9orf72 hexanucleotide repeat length distribution in 3142 Finns and study the association of intermediate repeat alleles with AD and cognitive impairment.

2. Methods

2.1. Cohorts

We studied the C9orf72 hexanucleotide repeat length in 3161 individuals from 4 population-derived cohorts from the Helsinki region in Southern Finland. These were the Vantaa 85+ study (Tanskanen et al., 2017) (n = 469), Helsinki Birth cohort study (Barker et al., 2005; Eriksson et al., 2006; Kajantie et al., 2012; Lahti et al., 2005; Eriksson et al., 2006; Kajantie et al., 2012; Lahti et al., 2014; Yliharsila et al., 2007) (n = 1651), Helsinki Businessmen study (Strandberg et al., 2016) (n = 666), and DEBATE study (Uusvaara et al., 2013) (n = 375). We have previously used the same cohorts to study the association of TYR0PB deletion and cognitive impairment (Kaiwola et al., 2018). Information on AD, other dementia diagnoses, mini mental state examination (MMSE) scores, or lack of dementia was assessed from clinical records, death certificates, registry information, or questionnaires. The source of information varied between cohorts. More detailed cohort descriptions and information on assessment of dementia are provided in the Supplementary Methods.

We studied the effect of intermediate repeat alleles in 3 settings: (1) individuals with AD versus no AD; (2) individuals with cognitive impairment (MMSE score <24) versus individuals with no cognitive impairment (MMSE score ≥24), and (3) individuals with cognitive impairment or any diagnosis of dementia versus nondemented controls. All controls were ≥75 years. Repeat lengths 7–45 and 20–45 were used as the definition of intermediate length alleles.

2.2. Genetic analyses

We determined repeat lengths with RP-PCR as previously described (Renton et al., 2011) with minor changes to the protocol (Supplementary methods). Because it may be difficult to distinguish between an expansion and a long repeat in RP-PCR, we confirmed alleles with repeat length ≥20 and all putative expansions with over-the-repeat PCR. Samples with more than 30 repeats and the typical sawtooth pattern in RP-PCR, which only produced the smaller amplicon in over-the-repeat PCR, were categorized as expansions (Supplementary Fig. 1).

The smallest allele is here denoted as 2–3 repeats because 2 and 3 repeat alleles cannot be distinguished by RP-PCR. RP-PCR results may be inaccurate in distinguishing heterozygosity and homozygosity in certain allele combinations (especially 2–3/5 from 5/5 and 5/8 from 8/8). This can slightly increase the proportion of heterozygotes at the expense of homozygotes. Considering this uncertainty, we did not analyze cognitive measures separately in individuals homozygous for the intermediate alleles. There were no samples homozygous for the 20–45 repeat alleles in our cohorts. APOE was genotyped as previously described (Myllykangas et al., 1999).

2.3. Statistics

We used logistic regression to test for association between intermediate repeats in all 3 settings and used APOE ε4 carriership, age, and sex as covariates. We applied Bonferroni correction to take account of multiple test settings and set the statistical significance to p = 0.05/3 = 0.017. We used Kruskal-Wallis H test to determine if repeat length distributions differed between our 4 cohorts. All analyses were conducted with IBM SPSS statistics v.24 (IBM Corp. Released, 2016; IBM SPSS Statistics for Windows, Version 24.0. IBM Corp., Armonk, NY, USA).

Assuming AD prevalence of 10% in Finnish individuals aged over 75 years (Rahkonen et al., 2003), intermediate allele (>7 repeats) frequency of 17% based on our initial results, case-control ratio of 1:4, type 1 error rate 0.05 and relative risk of 1.5 with dominant effect, 201 cases were required for 80% power (Purcell et al., 2003) (Genetic power calculator, http://zzz.bwh.harvard.edu/gpc/ accessed 4.6.2018). From the 4 cohorts, we identified 226 individuals with AD, 432 with MMSE ≤24, and 613 with any diagnosis of dementia or cognitive impairment.

2.4. Ethics

The study was approved by the Coordinating Ethics Committee of the Helsinki University Central Hospital. The Vantaa 85+ study was also approved by the Ethics Committee of the Health Centre of the City of Vantaa.

3. Results

3.1. Repeat length distribution

We successfully determined repeat lengths in 3142/3161 (99.4%) individuals. There was no statistically significant difference in the repeat length distributions between cohorts [H (3) = 2.129, p = 0.55]. Repeat length distribution of all alleles is shown in Fig. 1. The repeat length distribution showed peaks in repeat numbers 2–3, 5, 8, and 10. The longest nonexpanded allele we could characterize with repeat-primed PCR and amplify with over-the-repeat PCR was 45 repeats. The longer allele was in the range of 7–45 repeats in 1036/3142 (33%) individuals, 20–45 in 56/3142 (1.8%), 30–45 in 12/3142 (0.3%), and expansion (>45 repeats) in 6/3142 (0.19%). All expansion carriers were from the largest (HBCS) cohort.

Interestingly, repeat lengths ≥20 were more common in Finland than reported elsewhere in previous large studies. To compare the frequency of ≥20 repeat lengths, we searched PUBMED for large population based (>1000 individuals) case-control studies (>1000 controls) with C9orf72 repeat length distribution available. Besides the original articles describing the repeat, we identified 9 articles (Beck et al., 2013, Cacace et al., 2013, Fahey et al., 2014, He et al., 2015, Kohli et al., 2013, Nuytemans et al., 2013, Rutherford et al., 2012, Theuns et al., 2014, van der Zee et al., 2013) but only 4 had enough detailed information on ≥20 repeats for comparison. In these 4 studies, the prevalence of ≥20 repeats was significantly lower than in Finland (all allelic frequencies <0.52% and all p < 0.019, Fisher’s exact test) (Table 1). Of the 9 studies, only 2 found expansion carriers in their control groups with carrier frequency of 1/5748 (p = 0.0095 vs. our Finnish sample, Fisher’s exact test) (Theuns et al., 2014) and 11/7579 (p = 0.60 vs. FIN) (Beck et al., 2013).
3.2. Intermediate repeat length alleles, Alzheimer’s disease, and cognitive impairment

Number of individuals in each cohort with or without AD/cognitive impairment is shown in Supplementary Table 1.

3.2.1. Alzheimer’s disease

We identified 226 individuals with AD (68–97 years, mean age 86, 58% female, 33% carried 7–45 repeats, 1.3% carried 20–45 repeats) and 893 controls (aged 75–101, mean age 83, 58% female, 33% carried 7–45 repeats, 1.3% carried 20–45 repeats). Intermediate repeat length alleles did not associate with AD when intermediate repeat threshold was ≥ 7 (p = 0.90) or ≥ 20 (p = 0.96). Age (p = 3.8 × 10⁻¹⁰, odds ratio [OR] 1.07, 95% confidence interval [CI] 1.05–1.10) and APOE ε4 carriage (p = 5.5 × 10⁻¹⁰, OR 2.69, CI 1.97–3.68) were statistically significantly associated with AD but sex was not (p = 0.45).

3.2.2. MMSE scores

When individuals were divided based only on MMSE score into cases (MMSE score ≤ 24, n = 432, aged 61–99, mean age 85, 75% female, 27% carried 7–45 repeats, 1.6% carried 20–45 repeats) and controls (MMSE score ≥ 25, n = 719, aged 75–98, mean age 80, 38% female, 33% carried 7–45 repeats, 1.3% carried 20–45 repeats), there was a nominally significant association between 7–45 repeats and better cognition (p = 0.025, OR 0.71 for cognitive impairment, CI 0.53–0.96), but the association did not remain statistically significant after Bonferroni correction. This association disappeared when repeat length ≥ 20 was used as threshold for intermediate repeat allele (20–45 repeats, p = 0.72). Age (p = 5.0 × 10⁻¹⁰, OR 1.1, CI 1.1–1.2), female sex (9.8 × 10⁻¹⁴, OR 3.1, CI 2.3–4.1), and APOE ε4 carriage (p = 0.00078, OR 1.7, CI 1.2–2.2) associated significantly with cognitive impairment.

3.2.3. Any diagnosis of dementia or cognitive impairment

We identified 613 cases (aged 62–101, mean age 86, 65% female, 29% carried 7–45 repeats and 1.3% carried 20–45 repeats) and 1115 controls (aged 75–101, mean age 83, 37% female, 34% carried 7–45 repeats and 1.5% carried 20–45 repeats). There was a nominally significant association between intermediate repeat lengths and protection from dementia or cognitive impairment (p = 0.032, OR 0.78, CI 0.62–0.98), but this result was not statistically significant after Bonferroni correction, and again, the association was lost when intermediate repeat threshold ≥ 20 was used (20–45 repeats, p = 0.62). Age (p = 5.6 × 10⁻¹⁸, OR 1.08, CI 1.06–1.1), female sex

![Fig. 1. Repeat length distribution of all alleles in 3142 Finns. “Exp” denotes expansion.](image-url)

### Table 1

<table>
<thead>
<tr>
<th>Population</th>
<th>Number of individuals</th>
<th>Number of ≥20 repeats (expansions excluded)</th>
<th>Allelic frequency of ≥20 repeats (%)</th>
<th>p-value versus our sample</th>
<th>Expansions in controls (n)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Finnish</td>
<td>3142</td>
<td>56</td>
<td>0.89</td>
<td></td>
<td>6</td>
<td>This study [Beck et al., 2013]</td>
</tr>
<tr>
<td>British 1958 birth cohort</td>
<td>7577</td>
<td>64*</td>
<td>0.42</td>
<td>0.00051</td>
<td>11</td>
<td>[Fahey et al., 2014]</td>
</tr>
<tr>
<td>Irish</td>
<td>1234</td>
<td>10</td>
<td>0.41</td>
<td>0.019</td>
<td>0</td>
<td>[Theuns et al., 2014]</td>
</tr>
<tr>
<td>European/Asian/North American/Australian</td>
<td>5886</td>
<td>61 (≥17 repeats)</td>
<td>0.52</td>
<td>0.0045</td>
<td>1</td>
<td>[Rutherford et al., 2012]</td>
</tr>
<tr>
<td>North American</td>
<td>1444</td>
<td>11</td>
<td>0.38</td>
<td>0.0078</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

* Written personal communication from Professor Mead.
cofactors. The smallest expansions that segregate with combinations of ALS, FTD-ALS, and FTLD or dementia are found in 0.38% (1 per 262) individuals, and they did not have any apparent clustering of neurodegenerative or psychiatric diagnoses. A summary of carriers of 30−45 repeats and expansions is shown in Table 2.

4. Discussion

The C9orf72 hexanucleotide repeat expansion is a major cause of ALS/FTD; however, which repeat lengths are pathogenic is still unclear. Our data on 3142 older individuals show that 30−45 repeats are found in 0.38% (1 per 262) individuals, and they did not have any apparent clustering of neurodegenerative or psychiatric disease. Our data suggest that 30−45 repeat alleles should not be considered unequivocally pathogenic and other risk factors than the C9orf72 expansion should be considered in patients with these alleles. The smallest expansions that segregate with combinations of ALS, FTD-ALS, and “FTLD or dementia” are reportedly ca. 55–100 repeats as measured by Southern blot (Gijselinck et al., 2016). However, an individual with 70 repeats without neurodegeneration at the age of 90 years has been reported (McGoldrick et al., 2018). More data are still needed for more precise estimation of the pathological threshold, which may actually turn out as a “gray zone” where disease penetrance is dependent on modulating cofactors.

Our data are in line with previous studies indicating a lack of major association between intermediate repeats and AD. Sometimes, there was a nominally significant association between 7−45 repeat length alleles and better cognition. This association was not statistically significant in any of the individual cohorts and was only seen in the pooled data set. This can be a spurious association, but nevertheless, it supports the hypothesis that ≥7 repeat alleles do not predispose to cognitive impairment or dementia. Across all our cohorts, there was heterogeneity in sex and age distributions, variation in socioeconomic status, and educational history (one cohort consisted solely of men with high socioeconomic status), and there was no uniform way of defining cognition and dementia status, and this information was collected from several sources. Despite these limitations, we found a clear association between APOE ε4 genotype and AD (p = 5.5 × 10−10, OR 2.69), cognitive impairment (p = 0.00078, OR 1.7), and overall dementia status (p = 4.0 × 10−3, OR 1.8), which argues against a major bias in our definition of dementia. Furthermore, the Finnish national registers have been found to identify dementia cases accurately (Solomon et al., 2014).

None of the 6 expansion carriers we identified had a diagnosis of ALS or FTD but 4 had a diagnosis of a neurodegenerative or psychiatric disease. Two had died of coronary heart disease before the age of 70 years and others were under 80 years. Therefore, it is possible that some expansion carriers could have developed or may develop ALS/FTD in their later years.

Previous reports have shown that C9orf72 expansion is especially common cause of ALS/FTD in Finland (Majounie et al., 2012). In the present study, the expansion frequency in older Finns (median age 77) was only slightly higher than in the UK 1958 birth cohort. However, this UK population was considerably younger (age ca. 54–55 years during publication in 2013) than our Finnish sample. The penetrance of the C9orf72 expansion is known to be strongly age related; nearly complete penetrance was observed by 83 years in a cohort of 1147 ALS and FTD cases. The median age of onset varied somewhat with phenotype but was estimated to be around 58 years (Murphy et al., 2017). Therefore, it can be expected that the expansion frequency in the UK cohort will markedly decrease by time. In line with age-related penetrance, the expansions were unequally distributed in our cohorts; all Finnish expansion carriers were from the HBCS cohort, whose participants were the youngest of the 4 cohorts (born 1934−1944, and registry information available up till December 31 of 2013, Supplementary methods). If we restrict the analysis to this cohort only, expansion prevalence would be 6/1644 (0.36% or 1 in 274) in Finland.

Interestingly, we found that nonexpanded repeat lengths ≥20 are roughly twice as common in Finland than in other reported populations (Table 1). This finding may have a connection with the

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**Table 2**

Summary of individuals with ≥30 repeats

<table>
<thead>
<tr>
<th>Individual number</th>
<th>Sex</th>
<th>Age at last information collection</th>
<th>Repeat length (shorter/longer allele)</th>
<th>Information on cognition</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Female</td>
<td>91</td>
<td>2/30</td>
<td>MMSE score 26&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>2</td>
<td>Male</td>
<td>70</td>
<td>2/31</td>
<td>MMSE score 29&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>3</td>
<td>Female</td>
<td>72</td>
<td>2/31</td>
<td>No dementia diagnoses&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>4</td>
<td>Male</td>
<td>85</td>
<td>5/31</td>
<td>MMSE score 28&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>5</td>
<td>Male</td>
<td>70</td>
<td>2/32</td>
<td>MMSE score 30&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>6</td>
<td>Male</td>
<td>81</td>
<td>2/34</td>
<td>MMSE score 29&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>7</td>
<td>Female</td>
<td>89</td>
<td>5/36</td>
<td>MMSE score 21&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>8</td>
<td>Male</td>
<td>71</td>
<td>2/40</td>
<td>MMSE score 30/No dementia or psychiatric diagnoses</td>
</tr>
<tr>
<td>9</td>
<td>Male</td>
<td>72</td>
<td>2/43</td>
<td>No dementia or psychiatric diagnoses</td>
</tr>
<tr>
<td>10</td>
<td>Female</td>
<td>77</td>
<td>2/45</td>
<td>MMSE score 29/No dementia or psychiatric diagnoses</td>
</tr>
<tr>
<td>11</td>
<td>Male</td>
<td>74</td>
<td>2/45</td>
<td>MMSE score 29/No dementia or psychiatric diagnoses</td>
</tr>
<tr>
<td>12</td>
<td>Female</td>
<td>73</td>
<td>8/45</td>
<td>MMSE score 29/No dementia or psychiatric diagnoses</td>
</tr>
<tr>
<td>13</td>
<td>Male</td>
<td>79</td>
<td>2/expansion</td>
<td>G20 (Parkinson disease, ICD-10), No psychiatric diagnoses.</td>
</tr>
<tr>
<td>14</td>
<td>Female</td>
<td>60&lt;sup&gt;a&lt;/sup&gt;</td>
<td>2/expansion</td>
<td>300.40 (depressive neurosis, ICD-8), 300.88 (other neurosis, ICD-8), No dementia diagnoses.</td>
</tr>
<tr>
<td>15</td>
<td>Female</td>
<td>71</td>
<td>2/expansion</td>
<td>G31.0 (local brain atrophy, ICD-10). No psychiatric diagnoses.</td>
</tr>
<tr>
<td>16</td>
<td>Male</td>
<td>68&lt;sup&gt;a&lt;/sup&gt;</td>
<td>5/expansion</td>
<td>No dementia or psychiatric diagnoses</td>
</tr>
<tr>
<td>17</td>
<td>Female</td>
<td>71</td>
<td>6/expansion</td>
<td>No dementia or psychiatric diagnoses</td>
</tr>
<tr>
<td>18</td>
<td>Female</td>
<td>74</td>
<td>8/expansion</td>
<td>291.20 (Alcoholic psychosis, ICD-8), No dementia diagnoses.</td>
</tr>
</tbody>
</table>

<sup>a</sup> Age of death, cause of death coronary artery disease.

<sup>b</sup> Psychiatric diagnoses were not available. RP-PCR chromatograms are provided in Supplementary Fig. 2.

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(p = 1.1 × 10−24, OR 3.0, CI 2.5−3.8), and APOE ε4 carriership (p = 4.0 × 10−7, OR 1.8, CI 1.4−2.2) associated significantly with dementia or cognitive impairment.

3.2.4. Neurodegenerative and psychiatric diagnoses

We did not find any evident clustering of neurodegenerative or psychiatric disease in the 12 (0.38%) individuals with 30−45 repeats (Table 2). There were 6 (0.19%) expansion carriers and none had diagnosis of ALS or FTD; 2 had died at ages of 60 and 68 years because of coronary artery disease. Of the 4 living individuals (aged 71−79 years), one had been diagnosed with Parkinson disease (G20, ICD-10) and another had a diagnosis of local brain atrophy (G31.0, ICD-10). A third had been diagnosed with “other alcoholic hallucinosis” (291.20, ICD-8) and a fourth with depressive neurosis and other neurosis (300.40 and 300.88, ICD-8). A summary of carriers of 30−45 repeats and expansions is shown in Table 2.
high frequency of C9orf72 expansion in Finland and raises the question whether the $\geq 20$ repeat alleles could be prone to germline instability and expansion in the offspring. In this scenario, the larger intermediate alleles would form a pool from which new expansions can be derived, a mechanism shown in families with sporadic Huntington’s disease and in Huntington’s disease CAG repeat knock-in mice (Goldberg et al., 1993; Myers et al., 1993; Wheeler et al., 1999). Somatic instability (mosaicism) of the expansion has been previously demonstrated (Dols-Icardo et al., 2014; Fratta et al., 2015) and at least one family has been described, in which an unaffected 90-year-old father had a 70-repeat allele in blood (pre-mutation), which was transmitted to 4 offspring, who all had expansion in blood DNA (McGoldrick et al., 2018). Whether the expansion was present in the father’s sperm could not be tested. However, mosaicism with large expansions was demonstrated in other tissues; therefore, it is likely that the expansion was present in sperm. As more than half of the Finnish patients with ALS with neurodegenerative syndromes and are more frequent than expected in the UK population. Am. J. Hum. Genet. 92, 345–353.


