C9orf72 repeat expansion does not affect the phenotype in primary progressive aphasia

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ABSTRACT

Primary progressive aphasia (PPA) forms the spectrum of language variants of frontotemporal lobar degeneration (FTLD), including three subtypes each consisting of distinctive speech and language features. Repeat expansion in *C9orf72* gene is the most common genetic cause of FTLD. However, thus far only little is known about the effects of the *C9orf72* repeat expansion on the phenotype of PPA. This retrospective study aimed at determining the differences between the PPA phenotypes of the *C9orf72* expansion carriers and non-carriers. Our results demonstrated no significant differences between these groups, indicating that the *C9orf72* repeat expansion does not substantially affect the phenotype of PPA.

INTRODUCTION

The language variants of frontotemporal lobar degeneration (FTLD), known as primary progressive aphasias (PPA), are a group of neurodegenerative diseases affecting particularly speech and language skills [1]**.** PPA includes three main variants – nonfluent (nfvPPA), semantic (svPPA) and logopenic (lvPPA) aphasia. NfvPPA is the most common subtype representing approximately 25% of the FTLD cases and characterized by agrammatism in language production [1,2]. In svPPA, the main features are anomia and difficulties in single-word comprehension and the phenotype is present in 20 – 25 % of the FTLD patients [1,2]. The lvPPA is the rarest subtype of the PPA phenotypes, characterized by language deficit influencing word retrieval and sentence repetition [1]. Approximately 17% of PPA patients have lvPPA as the main phenotype [3]. Neuropathologically the nfvPPA and svPPA are typically associated with the FTLD-type brain pathology, whereas the lvPPA variant is more often associated with Alzheimer`s disease-like pathology [4].

Repeat expansion in *C9orf72* gene is considered as the most common genetic cause of FTLD [5,6]. In general, the *C9orf72* repeat expansion is associated with the behavioral variant frontotemporal dementia (bvFTD) subtype or with FTLD with motor neuron disease, whereas it is estimated to be only a rare cause of pure PPA (approx. 1-6 %) [7-9]. In the case of bvFTD, the *C9orf72* repeat expansion has been reported to associate with psychiatric phenotypes, especially psychosis [10-12]. However, whether the *C9orf72* repeat expansion influences the phenotype of PPA patients still needs further research [13-16].

Consequently, the present retrospective study aimed at assessing differences in the clinical phenotype of the *C9orf72* repeat expansion carriers and non-carriers with PPA. Considering the rareness of these disorders, demographic information is also demonstrated.

MATERIALS AND METHODS

The study population consists of PPA patients with confirmed *C9orf72* repeat expansion status diagnosed at the Kuopio University Hospital between the years 1996 to 2016. The data were collected retrospectively from the patient records including information about demographics, symptoms, clinical examinations, neuropsychological assessment, speech-language pathology assessment, laboratory analyses, and neuroimaging from 18 patients. Speech and language skills were evaluated with Western Aphasia Battery (WAB) and neuropsychological skills with The Consortium to Establish a Registry for Alzheimer's disease neuropsychological battery (CERAD-NB).

The diagnoses were made retrospectively based on the classification of primary progressive aphasia and its variants [1]. The limit for the pathologically expanded *C9orf72* repeat was set at > 30 repeats [6]. Other FTLD-associated genes were not screened, because our previous studies have shown that these mutations are extremely rare in the Finnish population, likely due to the genetic isolation of the Finns [17-19].

Statistical analyses were performed with SPSS statistics 25 software and significance level was set at $p<0.05$. Continuous variables were compared with Mann-Whitney-U test and categorial variables with Fisher`s exact test due to the small sample size and non-parametric distribution of continuous variables.

RESULTS

The demographic data of the study groups is demonstrated in the Table 1. The *C9orf72* repeat expansion carriers and non-carriers did not significantly vary in terms of sex, years of education, age at onset, age at diagnosis, and/or disease duration from onset of symptoms.

Within the *C9orf72* repeat expansion carriers, the mean disease duration (time from onset to death) was slightly lower than within the non-carriers but the difference was not statistically significant. (Table 1).

A total of five patients were *C9orf72* repeat expansion carriers and 13 were non-carriers (Table 1). All of the 13 non-carriers met the clinical criteria for nfvPPA [1]. Within the *C9orf72* repeat expansion carriers, three participants fulfilled the clinical criteria for nfvPPA, and two did not meet the whole criteria explicitly for any PPA variant according to the patient records from the symptom onset to death. These patients, however, fulfilled the inclusion criteria for PPA according to Mesulam 2001 and were classified as PPA not otherwise specified (PPA-NOS). The two patients displaying PPA-NOS showed progressive language symptoms and both of them had impaired comprehension of syntactically complex sentences and word-finding difficulties. The patients did not have apraxia of speech or agrammatism and therefore they were not classified as nfvPPA. One of the patients had hallucinations as the first symptom and presented executive dysfunction at the diagnostic phase. The two PPA-NOS patients showed agitation and wandering after the diagnosis and they also had abnormal gag reflex at the late stage of the disease. Later on, one of the patients displayed also hyperorality, personality changes, and extrapyramidal symptoms (rigidity and hypo/bradykinesia).

All of the 18 PPA patients of the study cohort had neuroimaging results suggestive for PPA in the magnetic resonance imaging (MRI) or computed tomography of the brain (CT) of the brain, single photon emission computed tomography (SPECT)/ or fluorodeoxyglucose positron emission tomography (FDG-PET), thus resulting in a total of 16 nfvPPA and two PPA-NOS diagnoses, which were supported by imaging according to the current criteria [1,20]. More

detailed clinical characteristics of the patients and the distribution of the diagnoses supported by the imaging findings are presented in Table 2.

There were no statistically significant differences in the phenotype according to the clinical criteria of nfvPPA between the *C9orf72* repeat expansion carriers and non-carriers at the time of diagnostic phase. All of the 18 participants had spared single-word comprehension and object knowledge at the time of the diagnosis. Moreover, apraxia of speech and impaired comprehension of syntactically complex sentences were the most common symptoms in the clinical criteria. (Table 2).

The first symptoms of the PPA patients with a known *C9orf72* repeat expansion status are presented in Table 2. Both in the *C9orf72* repeat expansion carrier and in the non-carrier groups the most common initial symptom was word-finding difficulties (40 % and 38.5 %, respectively). Memory impairment and hallucinations were more common first symptoms among the *C9orf72* repeat expansion carriers, whereas among the non-carriers more diffuse symptoms as dizziness or collapses, fatigue and overall slowness as well as depression, apathy or inertia were also present. In total, there were no statistically significant differences between the repeat expansion carriers and non-carriers regarding the first symptoms.

At the time of the diagnostic phase, all of the *C9orf72* repeat expansion carriers and non-carriers had word-finding difficulties (Table 2). Furthermore, other language symptoms in addition to those listed in the clinical criteria of nfvPPA were poverty of speech, reading difficulties, writing difficulties and dysarthria. One non-carrier with dysarthria had nfvPPA and ALS.

A subset of non-carriers had also slowness of speech, impaired word repetition and mutism and these symptoms were not seen among the *C9orf72* repeat expansion carriers. Nonetheless, there were no statistically significant differences among the carriers and non-carriers in the initial language symptoms.

The Consortium to Establish a Registry for Alzheimer's disease neuropsychological battery (CERAD-NB) is a standardized test battery commonly used as a screening tool for detecting memory diseases [21,22]. All subtest scores for both groups were below the cutoff values indicating cognitive impairment [23]. However, the subtest scores of CERAD-NB did not show statistically significant differences between the *C9orf72* repeat expansion carriers and non-carriers (Table 3). Verbal fluency and MMSE scores were lower in *C9orf72* repeat expansion carriers than in non-carriers, however the difference was not statistically significant between the groups.

We did not detect prominent differences in psychiatric features in the *C9orf72* repeat expansion carriers compared to non-carriers. Hallucinations were a first symptom for one carrier and one non-carrier had hallucinations at the time of the diagnostic phase. As for depression, one non-carrier had depression as a first symptom.

DISCUSSION

Here, we analyzed the language features and demographic characteristics of PPA patients with and without the *C9orf72* repeat expansion. Although *C9orf72* repeat expansions are rare in patients with PPA (approx. 1-6 % in other cohorts [7-9]), we found that a considerable percentage (28 %) of the patients in the present Finnish PPA cohort were expansion carriers, likely reflecting the high prevalence of the *C9orf72* repeat expansion in Finland in general

[6,24]. The main findings of the present study reveal that there may not be statistically significant or clinically relevant differences in the demographics, language symptoms or in the CERAD- test battery performance between the *C9orf72* repeat expansion carriers and non-carriers. Notably, disease duration, verbal fluency and MMSE scores were slightly lower in the carriers, but the results were not statistically significant. Additionally, cognitive deficits were detected in all subtests of the CERAD-NB among nfvPPA patients showed, indicating that the phenotype of PPA among the *C9orf72* repeat expansion carriers and non-carriers is not exclusively limited to language deficits.

Word-finding difficulty was the most common first symptom among the PPA participants despite the genetic background. In addition, the most common features of speech in general were apraxia of speech and impaired comprehension of syntactically complex sentences when regarding the prevailing clinical criteria of nfvPPA.

Studies related to bvFTD have indicated different phenotypes between the *C9orf72* repeat expansion carriers and non-carriers, with especially psychotic symptoms being more prevalent in patients with the *C9orf72* repeat expansion [10,12,25]. In the present study the phenotypes between the repeat expansion carriers and non-carriers did not show differences in PPA patients. Regarding the linguistic symptoms in bvFTD patients, a prior study showed lower scores in verbal fluency [26]. Accordingly, our present study found a trend towards more severely impaired verbal fluency also in PPA patients with the *C9orf72* repeat expansion, but with the limited cohort size, the difference was statistically non-significant.

Word-finding difficulty is one of the first symptoms of PPA [27,28] and it was found to be the most common first symptom also in the present study. A recent meta-analysis demonstrated signs of agrammatism or apraxia of speech in a majority of nfvPPA participants however there

has been a substantial variation in the prevalence of dysarthria among nfvPPA patients in different studies (18 % – 60 %) [29]. Similarly, in our study, apraxia of speech was a frequently documented symptom (66.7 %) and the prevalence of dysarthria was low (11.1 %).

According to the review by Rohrer and colleagues, patients with PPA who carried the *C9orf72* repeat expansion had predominantly the nfvPPA clinical syndrome, whereas the other two subtypes (svPPA and lvPPA) were rare among these carriers [16]. On the other hand, the study by Galimberti and colleagues described two patients with the svPPA syndrome in their cohort of 29 *C9orf72* repeat expansion carriers, without any patients with the nfvPPA phenotype [14]. In our study none of the patients had svPPA or lvPPA. Thus, these data altogether suggest that the nfvPPA is the most common PPA clinical phenotype in the *C9orf72* repeat expansion carriers, whereas the *C9orf72* repeat expansion-associated svPPA is rare.

The main strength of this study is the careful and thorough examination of all the patients at the neurological outpatient clinic by experienced neurologists. The limitations are the nature of the retrospective study and a small cohort group of PPA patients. However, PPA caused by the *C9orf72* repeat expansion is rare, and our study provides the largest characterization of the *C9orf72* repeat expansion-associated PPA so far. The comparisons between the groups, however, should be interpreted with caution, as there is a possibility of false negative results due to the limited statistical power. We did not further adjust the statistical analyses for multiple comparisons, as the initial analyses revealed no significant differences between the groups (i.e. adjusting for the risk of false positive was not relevant).

In conclusion, the findings of this study suggest that the *C9orf72* repeat expansion does not significantly affect the phenotype in PPA. Future studies with larger well-characterized patient cohorts are needed to evaluate the impact of the *C9orf72* repeat expansion in PPA further.

Considering the rareness of the *C9orf72* repeat expansion-associated PPA, international collaboration is needed to obtain larger cohorts in the future.

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CONFLICTS OF INTEREST

The authors have no conflict of interest to report.

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Table 1. Demographics of the study participants.

	All patients with confirmed *C9orf72* status	***C9orf72* +**	***C9orf72* -**	**p value**
N	18	5	13	
Gender: male, N (%)	6 (33.3%)	2 (40.0%)	4 (30.8%)	1.000
Education[1] (years)	9 – 14 median 12 IQR 5	9 – 14 median 12 IQR 4	9 – 14 median 12 IQR 5	0.661
Age at onset of symptoms (years)	53.1– 79.3 median 66.3 IQR 10.6	62.2 – 78.1 median 65.0 IQR 11.3	53.1 – 79.3 median 67.7 IQR 13.5	0.924
Age at diagnosis (years)	57.1 –80.4 median 68.0 IQR 12.5	63.1 – 79.7 median 67.2 IQR 11.6	57.1 – 80.4 median 68.3 IQR 14.0	0.924
Age at death (years)	61.0 –85.9 median 75.3 IQR 14.5 (N=14)	67.2 – 81.5 median 68.6 IQR - (N=3)	61.0 – 85.3 median 76.1 IQR 14.1 (N=11)	0.368
Duration from the onset to diagnosis (years)	0.3 – 5.2 median 2.2 IQR 2.0	0.3 – 2.9 median 2.2 IQR 1.7	0.7 – 5.2 median 2.2 IQR 3.0	0.566
Duration from the onset to death (years)	2.3 – 13.9 median 5.4 IQR 4.8	3.4 – 5.0 median 3.8 IQR -	2.3 – 13.9 median 6.3 IQR 4.0	0.170

IQR = Interquartile Range. [1] = Educational data was missing for two participants. P value refers to the significance between the *C9orf72* repeat expansion carrier (*C9orf72+)* and non-carrier (*C9orf72*-) groups.

Table 2. Clinical characteristics of the study participants.

	All patients with confirmed *C9orf72* status	***C9orf72* +**	***C9orf72* -**	**p value**
Imaging-supported diagnosis				
NfvPPA, N (%)	16 (88.9%)	3 (60.0%)	13 (100.0%)	0.065
PPA-NOS, N (%)	2 (11.1%)	2 (40.0%)	0 (0.0%)	0.065
Clinical criteria for nfvPPA				
Apraxia of speech, N (%)	12 (66.7%)	2 (40.0%)	10 (76.9%)	0.268
Agrammatism, N (%)	4 (22.2%)	1 (20.0%)	3 (23.1%)	1.000
Spared single-word comprehension, N (%)	18 (100.0%)	5 (100.0%)	13 (100.0%)	-
Impaired comprehension of syntactically complex sentences, N (%)	11 (61.1%)	3 (60.0%)	8 (61.5%)	1.000
Spared object knowledge, N (%)	18 (100.0%)	5 (100.0%)	13 (100.0%)	-
First symptoms				
Memory impairment, N (%)	4 (22.2%)	2 (40.0%)	2 (15.4%)	0.533
Hallucinations, N (%)	1 (5.6%)	1 (20.0%)	0 (0.0%)	0.278
Depression, N (%)	1 (5.6%)	0 (0.0%)	1 (7.7%)	1.000
Apathy or inertia, N (%)	1 (5.6%)	0 (0.0%)	1 (7.7%)	1.000
Fatigue, N (%)	2 (11.1%)	0 (0.0%)	2 (15.4%)	1.000
Dizziness or collapse, N (%)	3 (16.7%)	0 (0.0%)	3 (23.1%)	0.522
Overall slowness, N (%)	1 (5.6%)	0 (0.0%)	1 (7.7%)	1.000
Word-finding difficulties, N (%)	7 (38.9%)	2 (40.0%)	5 (38.5%)	1.000
Initial language symptoms[1]				

Word finding difficulties, N (%)	18 (100.0%)	5 (100.0%)	13 (100.0%)	-
Slowness of speech, N (%)	5 (27.8%)	0 (0.0%)	5 (38.5%)	0.249
Impaired word repetition, N (%)	5 (27.8%)	0 (0.0%)	5 (38.5%)	0.249
Poverty of speech, N (%)	10 (55.6%)	2 (40.0%)	8 (61.5%)	0.608
Impaired comprehension, N (%)	11 (61.1%)	3 (60.0%)	8 (61.5%)	1.000
Reading difficulties, N (%)	6 (33.3%)	1 (20.0%)	5 (38.5%)	0.615
Writing difficulties, N (%)	6 (33.3%)	1 (20.0%)	5 (38.5%)	0.615
Dysarthria, N (%)	2 (11.1%)	1 (20.0%)	1 (7.7%)	0.490
Mutism, N (%)	1 (5.6%)	0 (0.0%)	1 (7.7%)	1.000

[1]=Language symptoms at the diagnostic phase. P value refers to the significance between the *C9orf72* repeat expansion carrier (*C9orf72+)* and non-carrier (*C9orf72*-) groups.

Table 3. CERAD subtest scores of the study participants.

	All patients with confirmed *C9orf72* status	***C9orf72* +**	***C9orf72* -**	**p value**
Verbal fluency, median (IQR) N	5.5 (8.0) N=14	4.0 (5.0) N=5	7.0 (12.0) N=9	0.112
Naming test, median (IQR) N	7.5 (6.0) N=14	8.0 (5.0) N=5	7.0 (8.0) N=9	0.898
MMSE, median (IQR)	19.0 (8.0) N=14	16.0 (11.0) N=5	21.0 (7.0) N=9	0.147
Word list learning, median (IQR) N	9.0 (5.0) N=11	9.0 (14.0) N=4	9.0 (5.0) N=7	1.000
Constructional praxis, median (IQR) N	8.0 (3.0) N=11	8.0 (2.0) N=4	9.0 (3.0) N=7	0.788
Word list delayed recall, median (IQR) N	3.0 (3.0) N=11	1.5 (6.0) N=4	3.0 (1.0) N=7	0.315
Word list delayed recall %, median (IQR) N	66.0 (38.0) N=11	69.0 (85.0) N=4	66.0 (30.0) N=7	1.000
Word list recognition %, median (IQR) N	75.0 (40.0) N=11	60.0 (80.0) N=4	80.0 (25.0) N=7	0.315
Constructional praxis delayed, median (IQR) N	6.0 (6.0) N=9	7.0 (-) N=3	5.0 (8.0) N=6	0.714
Constructional praxis delayed %, median (IQR) N	62.0 (74.0) N=10	56.5 (76.0) N=4	62.0 (75.0) N=6	0.610
Clock drawing, median (IQR) N	2.5 (2.0) N=9	3.0 (3.0) N=4	2.0 (3.0) N=5	0.905

IQR = Interquartile Range. P value refers to the significance between the *C9orf72* repeat expansion carrier (*C9orf72+)* and non-carrier (*C9orf72*-) groups.