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Title: Frontotemporal Dementia in Russia: Genetic Structure, Phenotypic Diversity, and Diagnostic Biomarkers

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Abstract

Introduction: Frontotemporal dementia (FTD) is a heterogeneous group of diseases with complex clinical picture, including cognitive decline, behavioral and speech problems, psychiatric symptoms, parkinsonism, etc. Diagnosis of FTD is difficult and requires the use of informative biomarkers.

Methods: We examined 226 Russian patients with FTD (mean age 69±10 years) and estimated the prevalence of the three most common genetic causes – mutations in the *C9orf72*, *GRN* and *MAPT* genes. We also assessed the role of biochemical biomarkers, such as serum progranulin (PGRN) level and cerebrospinal fluid (CSF) levels of β-amyloid (Aβ)-42 and phosphorylated tau protein (p-tau181).

Results: Mutations in *C9orf72*, *GRN* and *MAPT* were present in 6%, 12.5% and 2.5% of patients, respectively. Clinical phenotypes of these patients were detailed described. Low serum PGRN could be used to predict *GRN*-associated FTD cases. In most cases we found normal CSF levels of Aβ-42 and p-tau181 except 6 who had decreased Aβ-42 levels and normal p-tau181 levels.

Conclusion: We have conducted the first study of the genetic structure of FTD in Russia, the results of which, in combination with other biomarkers, will help improve the diagnosis of the disease.

Key worlds: Frontotemporal dementia, *C9orf72*, *MAPT*, *GRN*, Serum progranulin, Aβ-42, p-tau181.

Introduction

Frontotemporal dementia (FTD), a heterogeneous clinical syndrome corresponding to underlying frontotemporal lobar degeneration (FTLD), is one of the most common causes of dementia with early onset (Snowden et al., 2011). The annual incidence of FTLD in Europe is 2.36 cases per 100 000 person-years, with the maximum peak of 13.09 cases per 100 000 person-year at the age of 71 (Logroscino et al., 2023).

Typical clinical phenotypes of FTD include behavioral variant (bvFTD) (Rascovsky et al., 2011) and different variants of primary progressive aphasia: non-fluent (nfvPPA), semantic (svPPA) and logopenic (lvPPA) (Gorno-Tempini et al., 2011). Cognitive, behavioral and language symptoms are often accompanied by parkinsonism (Rowe, 2019) and amyotrophic lateral sclerosis (ALS) (Ng, Rademakers, & Miller, 2015). In Europe bvFTD represents the most common phenotype, followed by different variants of PPA, FTD-parkinsonism and FTD-ALS (Logroscino et al., 2023). About 30% of FTD patients have a positive family history (Logroscino et al., 2023). The greatest contribution to the development of FTD is made by genes *C9orf72*, *MAPT* and *GRN*, and the frequency of the corresponding mutations varies in different regions and populations (Moore et al., 2020).

FTD motor symptoms and speech phenotypes frequent overlap with other neurodegenerative diseases like Alzheimer's disease (AD) and atypical parkinsonism syndromes (Alladi et al., 2007; Deutschländer et al., 2018). Behavioral symptoms of FTD often difficult to differentiate with primary psychiatric diseases (Ducharme et al., 2020). These difficulties can delay FTD diagnosis by several years, so the introduction of genetic testing and other reliable biomarkers of this disease is of great importance (Ducharme et al., 2020).

Except genetic testing other biological biomarkers for FTD are absent. Among FTD patients, a progranulin glycoprotein (PGRN) level in biological fluids could be used for detection of *GRN* mutation carriers (Antonell et al., 2012). Assessment of AD biomarkers in cerebrospinal fluid (CSF) in FTD are considered as potential option for more accurate excluding of AD pathology in FTD syndromes (Paraskevas et al., 2017; Casoli et al., 2019), but interpretation of these results could be complicated. On the one hand in some pathological series AD as the primary pathological diagnosis was established among 7.1% patients with phenotype bvFTD, 44.1% with nfvPPA, 10% with svPPA and 74.1% with mixed aphasia (Alladi et al., 2007). But on the other data among uncommon AD phenotypes positivity on amyloid biomarker could also be considered as comorbid to another primary pathology (De Wilde et al., 2019; Naasan et al, 2016).

In the Russian population, there are no data on the incidence and prevalence of FTD, frequency of common genetic variants and role of fluid biomarkers in diagnosis. The aim of our

study was to evaluate the phenotypic spectrum and genetic structure of FTD in a large cohort of Russian patients, as well as to assess the role of serum and cerebrospinal fluid (CSF) biomarkers that can be potentially used for the diagnosis.

Material and methods

Characteristics of the studied cohort

In our study we used the local register of patients with FTD at the Department of Neurogenetics, Research Center of Neurology, Moscow. The study was approved by the Local Ethics Committee of Research Center of Neurology (protocol number 13-2/17). The database comprised clinical information on 226 patients with FTD (126 women and 100 men, mean age 69±10 years (range 34–84), mean age of onset 62±10 years (31–83)). The phenotypical spectrum was presented by bvFTD (n=103), nfvPPA (n=46), svPPA (n=20), lvPPA (n=5) and undifferentiated forms of FTD and PPA (n=52). A positive family history was recorded for 65 patients (29%), and for 47 patients (21%) family history information was not available. All patients signed an informed voluntary consent for the study.

Genetic testing

Genetic testing for the GGGGCC repeat expansion in the *C9orf72* gene was performed in 193 patients. We used fragment analysis with repeated primed PCR as described earlier (Lysogorskaia et al., 2016). The studied group was presented by bvFTD (n=85), nfvPPA (n=40), svPPA (n=14), lvPPA (n=5) and undifferentiated form of FTD (n=49). The mean age of the disease onset was 61±9 years (range 35–80); 78 patients (40%) had positive family history.

Genetic testing for the *GRN* and *MAPT* genes point mutations was performed in 80 patients using Sanger sequencing or massive parallel sequencing with our original "neurodegeneration" panel followed by Sanger sequencing confirmation. The group was presented by bvFTD (n=31), nfvPPA (n=22), svPPA (n=3), lvPPA (n=2) and undifferentiated form of FTD (n=22). The mean age of the disease onset was 59±11 years (range 31–80); 35 patients had positive family history (43%). We also analyzed *GRN* and *MAPT* deletions and duplications in 50 patients (26 familial and 24 sporadic cases) by multiplex ligation-dependent probe amplification (MLPA) method (SALSA MLPA P275-C3, MRC-Holland, Netherlands) using the standard protocol. Polymerase chain reaction (PCR) products were separated by size with capillary electrophoresis using genetic analyzer Nanofor 5 (Syntol, Russia). The analysis of result was performed with GeneMarker V3.0.1.

Serum PGRN level

Serum level of progranulin (PGRN), a product of *GRN* gene, was assessed in 19 FTD patients, including 5 carriers of *GRN* mutations. We used enzyme-linked immunosorbent assay (ELISA) using reagents Cloud Clone Corporation (USA, China) according to the manufacturer protocol. Since the level of PGRN can be influenced by various genetic factors, of which one of the most important is single nucleotide polymorphism (SNP) rs5848 in the *GRN* gene, in this work we assessed it by Sanger sequencing.

Alzheimer's disease (AD) biomarkers

We assessed AD biomarkers, β-amyloid (Aβ)-42 and phosphorylated tau protein (p-tau181), in CSF of 28 patients with FTD. The group was presented by bvFTD (n=16), nfvPPA (n=5), svPPA (n=3) and lvPPA (n=4). CSF biomarkers Aβ-42 (cutoff 600 pg/mL) and p-tau181 (cutoff 50 pg/mL) were analyzed using ELISA according to the manufacturer protocol.

Results

C9orf72 gene

The pathological GGGGCC repeat expansion in the *C9orf72* gene were found in 12 patients (6%), of which 8 had positive family history. Thus, the frequency of *C9orf72*-associated FTD among familial cases was 10%, and among sporadic cases – 3.5%. The mean age of onset was 56.5±11 years (range 38–77). Men and women were represented equally. Clinical phenotype in most cases (7/12) was a combination of behavioral/aphatic FTD with ALS, while other 5 cases were presented by "pure" bvFTD (n=3) and nfvPPA (n=2). Four patients also had parkinsonism with bradykinesia and muscle rigidity, and 5 patients had some other neurological signs, such as myoclonus, tremor (of the hands or head), and apraxia of swallowing. Apathy was the most common affective symptom (half of the cases), followed by depression, euphoria, disinhibition, and OCD. One patient with bvFTD and OCD also had frequent episodes of cognitive fluctuations with episodes of apathy and severe speech disturbances lasting up to several days ("Lewy body disease"-like phenotype).

GRN gene

We identified 6 different *GRN* mutations in 10 unrelated patients (12.5% in our FTD cohort). Three variants were previously described as pathogenic: c.102del (p. Gly35fs) in exon 2 (4 patients), c.328C>T (p.Arg110*) in exon 4 (1 patient) and c.933+1G>A in the splice donor site (1 patient). We found 2 new frameshift deletions (both in exon 9) that could be interpreted as pathogenic: c.945_946del (p.Cys315fs) in 1 patient and c.1150delG (p.Gly384fs) in 2 patients.

We also found a variant c.1735C>T (Arg579Cys) (rs748764855) in exon 12 with uncertain significance (VUS). This variant has low minor allele frequency (MAF) (T=0.000007, 1/140270, GnomAD; T=0.000025, 3/119780, ExAC) and was interpreted as "dangerous" with the SIFT program.

No deletions or duplications of *GRN* exons were found.

All *GRN* mutations identified in our cohort are shown in **Figure 1.**

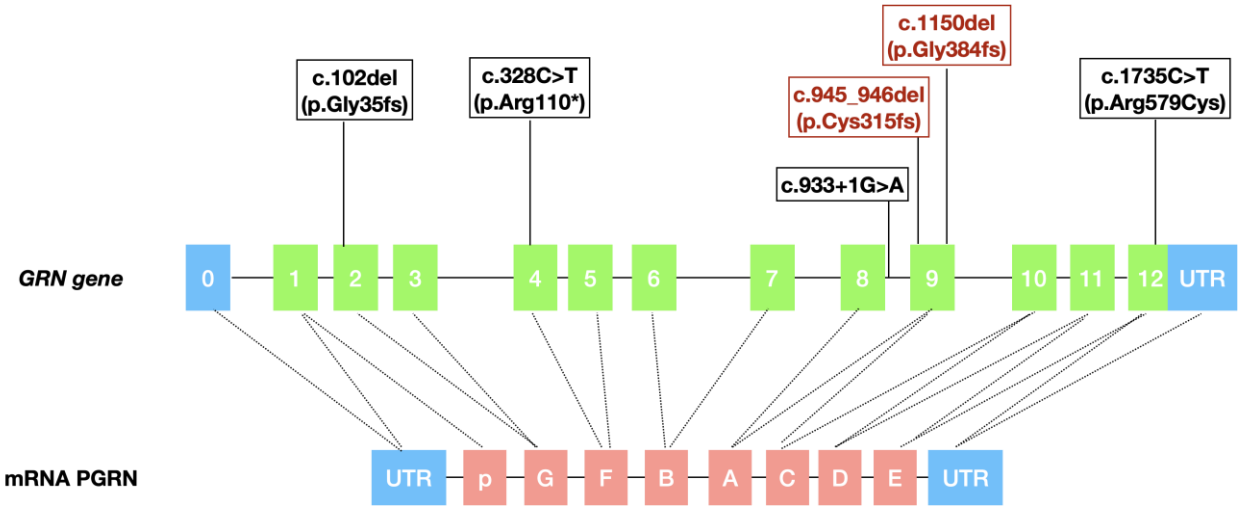

Figure 1. Localization of *GRN* mutations in a Russian cohort of patients with FTD.
GRN gene and mRNA PGRN are shown. *GRN* gene mutations identified in the study located in corresponding exon positions. Red color indicates new undescribed earlier variants.

Six of 10 patients had positive family history. Thus, the frequency of *GRN*-associated FTD among familial cases was 19% (6/32) and among sporadic cases – 8% (4/48). The mean age of onset was 57±8 years (47–71). Men and women were represented equally. The disease manifested in 5 cases with speech disorders (nfvPPA) and in 5 cases with behavioral problems (bvFTD). Half of the patients showed signs of parkinsonism (one of them with corticobasal syndrome). In addition, clinical picture of *GRN*-associated FTD cases included apraxia, postural hand tremor, myoclonus, postural instability, and dysphagia. Neuropsychiatric problems were presented mainly by apathy, appetite abnormalities and hyperphagia, less often one could see depression, anxiety, irritability and hypersomnia. Detailed clinical phenotypes of patients with *GRN* mutations are presented in Table 1.

Table 1. Clinical phenotype of patients with *GRN* mutations**.**

#	Mutation	Age of onset, yrs	Family history	Sex	Diagnosis	Other motor signs	Neuropsychiatric symptoms	Brain MRI
1	c.102del (p.Gly35fs)	53	negative	f	bvFTD	CBS	apathy, hyperphagia	frontotemporal atrophy D>S
2	c.102del (p.Gly35fs)	47	negative	m	bvFTD	bradykinesia	apathy, hyperphagia, hypersomnia	frontotemporal atrophy S>D
3	c.102del (p.Gly35fs)	71	positive	m	bvFTD	parkinsonism, hand rest tremor, freezing of gait, postural instability, dysphagia	apathy	frontotemporal, parietal atrophy S>D
4	c.102del (p.Gly35fs)	67	positive	f	nfvPPA	apraxia	apathy	frontotemporal, parietal, insular atrophy S>D
5	c.328C>T (p.Arg110*)	56	positive	m	bvFTD	bradykinesia, apraxia, cortical myoclonus	apathy, hypersomnia	frontotemporal atrophy S>D
6	c.933+1G>A	60	positive	f	nfvPPA	parkinsonism, apraxia, postural hand tremor	depression, anxiety, irritability	frontotemporal atrophy S>D
7	c.945_946del (p.Cys315fs)	47	negative	f	bvFTD	-	apathy, appetite abnormalities	frontotemporal atrophy D>S
8	c.1150del (p.Gly384fs)	53	positive	f	nfvPPA	-	apathy, appetite abnormalities	frontotemporal atrophy S>D
9	c.1150del (p.Gly384fs)	55	positive	m	nfvPPA	apraxia	apathy	frontotemporal, parietal atrophy S>D
10	c.1735C>T (p.Arg579Cys)	52	negative	m	nfvPPA	-	apathy, irritability, emotional lability	frontotemporal atrophy S>D

MAPT

We found 2 single nucleotide variants in the *MAPT* gene in our cohort of patients. One of them, c.1801C>G (p. Leu266Val) in exon 9, was previously described as pathogenic. A mutation carrier was a young male patient with negative family history and a phenotype of primary progressive apraxia of speech with onset at 35 years. In addition to severe speech problems with fast progression to mutism he had asymmetric apraxia and bradykinesia in the hands. Brain MRI showed asymmetric atrophy in the frontotemporal and parietal lobes with predominance on the right side.

The second variant c.1505C>T (p.Ser502Phe) was found in exon 6 of the *MAPT* gene. This variant has low MAF (T=0.001604, 225/140278, GnomAD; T=0.001458, 177/121412 ExAC), and Clinvar database interpreted it as VUS. A carrier was a female patient with positive family history and onset of bvFTD phenotype at the age of 74.

No deletions or duplications of *MAPT* exons were found.

Thus, the frequency of *MAPT* mutations in Russian cohort of FTD patient is low and represents 2.5%.

Serum PGRN

The serum PGRN levels in patients with exon mutations in the *GRN* gene were reduced compared to *GRN*-negative patients: 14 ng/ml [8;19] vs 31 [16; 45] ng/ml, respectively ($p<0.05$). Interestingly, patient with an intron *GRN* variant had a high PGRN level compared patients with exon mutations (Table 2). We found no associations of PGRN levels with clinical, demographic factors or rs5848 variants.

Table 2. Serum PGRN levels in patients with *GRN*-associated FTD.

#	*GRN* mutation	Position	Serum PGRN level	FTD form
1	c.102del (p.Gly35fs)	Exon 2	19 ng/ml	bvFTD
2	c.102del (p.Gly35fs)	Exon 2	6.9 ng/ml	bvFTD
8	c.1150del (p.Gly384fs)	Exon 9	10.5 ng/ml	nfvPPA
9	c.1150del (p.Gly384fs)	Exon 9	18 ng/ml	nfvPPA
6	c.933+1G>A	Splice	44 ng/ml	nfvPPA

AD biomarkers

In most cases we found normal CSF levels of Aβ-42 and p-tau181. However, 6 patients had decreased Aβ-42 levels and normal p-tau181 levels; among them, there were 3 patients with bvFTD, as well as one patient each with svPPA, lvPPA and nfvPPA.

Discussion

According to our data the most common genetic form of FTD in the Russian cohort of patients is a *GRN*-associated form (12.5%), followed by forms with mutations in *C9orf72* (6%) and *MAPT* (2.5%). The same distribution is characteristic for sporadic FTD (*GRN* – 8%, *C9orf72* – 3.5%, and *MAPT* – 2%) and for familial cases of the disease (*GRN* – 19%, *C9orf72* – 10% and *MAPT* – 3%). Among other populations, the closest data were obtained for the Italian, Portuguese, Belgian and Scandinavian cohorts (Moore et al., 2020).

Our cohort of *C9orf72*-associated cases phenotypically presented by bvFTD, nfvPPA and combination of behavioral/aphatic FTD with ALS (the most of cases). The most common motor symptoms except ALS-like were parkinsonism and hyperkinetic disorders. The most common psychiatric features were apathy followed by depression, euphoria, disinhibition and OCD. It is important to know that patients with the GGGGCC repeat expansion in the *C9orf72* gene have usually a high frequency of psychotic disorders, such as bipolar disorder, mania, major depressive episodes with catatonic features and OCD (Ducharme, Bajestan, Dickerson, & Voon, 2017). Those symptoms may precede typical FTD features by up to 4–5 years (Ducharme et al., 2017), which is a serious challenge for timely correct diagnosis. Thus, at the onset of FTD with affective disorders, the key to the correct diagnosis may be the identification of mild cognitive, speech and motor disorders which could serve as an indicator of the underlying FTLD. FTD patients carrying *C9orf72* mutations have previously been shown to have a higher frequency of psychiatric symptoms and are less prone to eating behavior disorders and the loss of empathy compared to *GRN* mutation carriers (Snowden et al., 2015). Our results support these observations.

We found 6 mutations in the *GRN* gene, and 2 of them were not described previously. Mutation p.Gly35fs is the most frequent in our patients with typical phenotypes bvFTD or nfvPPA associated with parkinsonism. Another known mutation p.Arg110* was found in our patient with an usual phenotype of bvFTD associated with parkinsonism and cortical myoclonus. We have shown for the first time that a previously described variant c.933+1G>A can be characterized by and unusual phenotype, nfvPPA with parkinsonism, while Moore et al. in their meta-analysis described in carriers of this mutation only bvFTD, an AD-like phenotype or CBS (Moore et al., 2020). We also found two variants (p.Cys315fs and p.Gly384fs) not previously described in the literature, and the p.Gly384fs variant was found in two unrelated patients with low serum levels of PGRN.

Data on the serum PGRN level in patients with *GRN*-associated FTD remain controversial. PGRN level has previously been shown to be a reliable biomarker to predict *GRN* mutations even in an asymptomatic stage of neurodegeneration, and it does not correlate with the

age of onset or clinical phenotype (Sellami et al., 2020). However, PGRN levels depend not only on *GRN* mutations, but also on some SNPs (G.-Y. R. Hsiung, Fok, Feldman, Rademakers, & Mackenzie, 2011) and the presence of other diseases (Körtvélyessy et al., 2015; Vercellino et al., 2011; Yamamoto et al., 2014). In our study serum PGRN levels were decreased in patients with exon point mutations in *GRN*, but not in a patient with the intron c.933+1G>A variant. One can conclude that clarification of the diagnostic and biomarker role of the serum PGRN level requires further studies.

We identified in our cohort only one previously described pathogenic mutation in the *MAPT* gene (Leu266Val). It is the first case of detection of a *MAPT* mutation in Russia. In another study, according to Moore et al., several patients with this mutation were observed with mean age of onset of 32.4 years and mean disease duration of 6 years (Moore et al., 2020). Most of described patients had the phenotype of bvFTD, one had svPPA and others had unspecified forms of dementia (Moore et al., 2020). Our patient had a typical age of onset but a unique clinical phenotype (fast progression of primary apraxia of speech and asymmetric apraxia/bradykinesia in the hands), which emphasizes phenotypic diversity of a *MAPT*-associated form of the disease.

According to the literature, only 1.5% of individuals with *GRN*-associated forms have exon deletions or duplications in the *GRN* gene (G. R. Hsiung & Feldman, 2020), while there is no data about exon rearrangements in the *MAPT* gene. Our results indicate that this type of mutations is not typical for Russian patients with FTD.

We found changes in CSF biomarkers in 20% of studied cases (3/16 with bvFTD, 1/4 with lvPPA, 1/3 with svPPA and 1/5 with nfvPPA). Our results are consistent with data of prevalence AD pathology and biomarkers AD positivity among patients with FTD-like phenotype (Alladi et al., 2017; Paraskevas et al., 2017). According to the current AD criteria, the diagnosis of AD is based on a combination of clinical phenotype and biomarker assessment (Dubois et al., 2021). lvPPA is a typical AD phenotype with prevalent presentation amyloid pathology in autopsy studies (Giannini et al., 2017), and its combination with Aβ-42 positivity could be regarded as ‘probable’ AD (Dubois et al., 2021). Interpretation of uncommon AD phenotypes like behavioral, svPPA and nfvPPA is more complicated, because their combination with Aβ-42 positivity could be regarded as ‘possible’ AD according IWG criteria (Dubois et al., 2021). But its unsolvable clinical situation because we do not yet have reliable markers of FTLD pathology, and in all these cases we don’t know is its primary AD pathology or co-existing AD pathology. In some works, discussed using combination of two amyloid biomarkers (CSF and amyloid-PET) in unclear cases (Giacomucci et al., 2021).

Conclusion

It is the first data presenting the phenotypic spectrum, genetic structure and biomarker assessment results in a large Russian cohort of FTD patients. Further studies may allow us to understand the prevalence of the FTLD pathology in Russia and identify specific characteristics of the disease facilitating early diagnosis. These data may also help to create algorithms for the differential diagnosis of FTD with other neurodegenerative dementias and, in the future, to find new therapeutic approaches and ways for the prevention of the disease in affected families.

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