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Research Paper

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 a complex clinical picture, including cognitive decline, behavioral and speech problems, psychiatric symptoms, and parkinsonism. Diagnosis of FTD is complex 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 amyloid β (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. The clinical phenotypes of these patients were described in detail. 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 for 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, combined with other biomarkers, will help improve the diagnosis of the disease.

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Highlights

• GRN- and C9orf72-associated frontotemporal dementia (FTD) are the most frequent genetic forms in Russia.

•Serum progranulin (PGRN) was low only in the FTD patients with exon mutations, not in those with intron mutations.

• It was found that 20% of Russian patients with various FTD phenotypes had amyloid positivity in their cerebrospinal fluid (CSF).

Plain Language Summary

FTD is very heterogeneous form of dementia with various clinical presentations (behavioral, speech, movement disorders) and high frequency of genetic causes. It is very difficult to diagnose, especially on the early stage of the disease. In Russia, there is no any large cohort study on this disease. Therefore, the main goals of this study are to describe more frequent clinical variants, assess frequency genetic forms, and assess other disease markers that can help diagnose FTD or rule out other diseases such as AD in Russian people. In our study we examined 226 Russian patients with different FTD variant. It was shown that mutation in GRN gene was more frequent in Russian patients. It was present in 12.5% of all patients, and in 19% of familial cases. We found two novel GRN mutations. We also found that special blood biomarker PGRN could predict pathogenicity of new GRN mutation which possibly indicate the necessity for genetic testing. The second most frequent genetic form in patients was C9orf72. It was present in 6% of all patients, and in 10% of familial cases. The most common form was MAPT. We also found that checking for Alzheimer's disease (AD) biomarkers in the cerebrospinal fluid of patients with FTD revealed that 20% of them had positive results.

1. Introduction

Frontotemporal dementia (FTD), a heterogeneous clinical syndrome corresponding to underlying frontotemporal lobar degeneration (FTLD), is one of the most common cause of dementia with early onset (Snowden et al., 2011). The annual incidence of FTLD in Europe is 2.36 cases per 100000 person-years, with the maximum peak of 13.09 cases per 100000 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 et al., 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 frequently overlap with other neurodegenerative diseases like Alzheimer disease (AD) and atypical parkinsonism syndromes (Alladi et al., 2007; Deutschländer et al., 2018). Behavioral symptoms of FTD are often challenging to differentiate from primary psychiatric diseases (Ducharme et al., 2020). These difficulties can delay FTD diagnosis by several years, so introducing genetic testing and other reliable biomarkers of this disease is very important (Ducharme et al., 2020).

Except for genetic testing, other biological biomarkers for FTD are absent. Among FTD patients, a progranulin glycoprotein (PGRN) level in biological fluids could be used to detect *GRN* mutation carriers (Antonell et al., 2012). Assessment of AD biomarkers in cerebrospinal fluid (CSF) in FTD is considered a 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% of patients with phenotype bvFTD, 44.1% with nfvPPA, 10% with svPPA, and 74.1% with mixed aphasia (Alladi et al., 2007). Nevertheless, among uncommon AD phenotypes, positivity on amyloid biomarkers could also be considered 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, the frequency of common genetic variants, and the role of fluid biomarkers in diagnosis. Our study aimed to evaluate the phenotypic spectrum and genetic structure of FTD in a large cohort of Russian patients and assess the role of serum and CSF biomarkers that can be potentially used for the diagnosis.

2. Materials and Methods

Characteristics of the studied cohort

Our study used the local register of patients with FTD at the Department of Neurogenetics, Research Center of Neurology, Moscow. 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 (range: 31–83). The phenotypical spectrum was presented by FTD (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 information on family history was unavailable for 47 patients (21%). 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 forms 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 the 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 forms of FTD (n=22). The mean age of the disease onset was 59±11 years (range 31–80); 32 patients had positive family history (40%). 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 the genetic analyzer Nanofor 5 (Syntol, Russia). The analysis of the result was performed with GeneMarker software, version 3.0.1.

Serum PGRN level

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

AD biomarkers

We assessed AD biomarkers, amyloid-β(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 of Aβ-42 (cutoff point, 600 pg/mL) and p-tau181 (cutoff point, 50 pg/mL) were analyzed using ELISA according to the manufacturer's protocol.

3. Results

C9orf72 gene

The pathological GGGGCC repeat expansion in the *C9orf72* gene was found in 12 patients (6%), of which 8 had a 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 the 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 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).

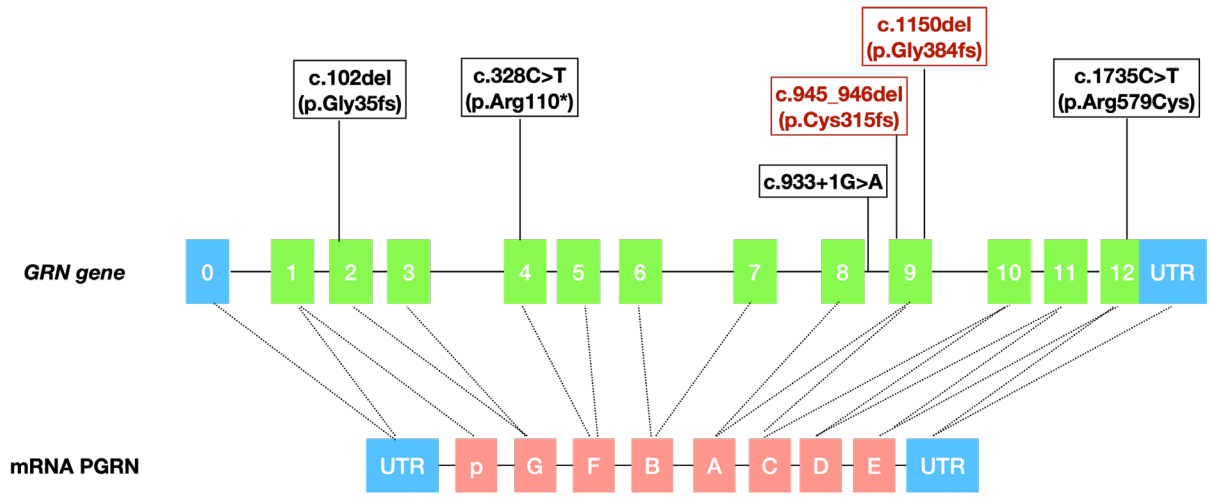

Figure 1. Localization of *GRN* mutations in a Russian cohort of patients with frontotemporal dementia NEUROSCIENCE

Notes: *GRN* gene and mRNA PGRN are shown. *GRN* gene mutations identified in the study are located in corresponding exon positions. The red color indicates new, undescribed variants.

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.

Six of 10 patients had a 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 5with behavioral problems (bvFTD). Half of the patients showed signs of parkinsonism (one of them with corticobasal syndrome). In addition, the 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.

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 a 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 a 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 the Russian cohort of FTD patients is low and represents 2.5%.

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

#	Mutation	Age of Onset (y)	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

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Serum PGRN

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

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 and one patient each with svPPA, lvPPA, and nfvPPA.

4. 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 a combination of behavioral/aphatic FTD with ALS (most 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 Obsessive compulsive disorder (OCD). It is important to know that patients with the GGGGCC repeat expansion in the *C9orf72* gene usually have a high frequency of psychotic disorders, such as bipolar disorder, mania, major depressive episodes with catatonic features, and OCD (Ducharme et al., 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

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

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

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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 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 a 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 an unusual phenotype, nfvPPA with parkinsonism, while Moore et al. (2020), in their meta-analysis described in carriers of this mutation only bvFTD, an AD-like phenotype or CBS. 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 remains 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 (Hsiung, et al., 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 decreased in patients with exon point mutations in *GRN* but not in patients 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.

Our cohort identified 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. (2020), several patients with this mutation were observed with a mean age of onset of 32.4 years and a mean disease duration of 6 years. Most of the 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 the 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 (Hsiung & Feldman, 2020), while there is no data about exon rearrangements in the *MAPT* gene. Our results indicate that this type of mutation 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 on AD pathology prevalence and AD biomarkers 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 a prevalent presentation of 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). Interpreting 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 to IWG criteria (Dubois et al., 2021). Nevertheless, it is an unsolvable clinical situation because we do not yet have reliable markers of FTLD pathology, and in all these cases, we do not know whether it is its primary AD pathology or co-existing AD pathology. Some works discussed using a combination of two amyloid biomarkers (CSF and amyloid-PET) in unclear cases (Giacomucci et al., 2021).

5. 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 FTLD pathology in Russia and identify specific disease characteristics, 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.

Ethical Considerations

Compliance with ethical guidelines

This study was approved by the Local Ethics Committee of the Research Center of Neurology, Moscow, Russia (Code: 13-2/17).

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Authors' contributions

Conceptualization and supervision: Sergey Illarioshkin and Ekaterina Fedotova; Methodology: Ekaterina Fedotova and Yulia Shpilyukova; Data collection: Yulia Shpilyukova; Data analysis: Yulia Shpilyukova, Natalia Abramycheva and Alla Shabalina; Investigation, and writing the original draft: Yulia Shpilyukova; Review and editing: All authors.

Conflict of interest

The authors declared no conflict of interest.

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