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Frequency of frontotemporal dementia-related gene variants in Turkey

Sevilhan Artan[a,#], Ebru Erzurumluoglu Gokalp[a,#,*], Bedia Samanci[b], Demet Ozbabalik Adapinar[c], Hasan Bas[a], Fatih Tepgec[d], Emilia Qomi Ekenel[a], Oguz Cilingir[a], Basar Bilgic[b], Hakan Gurvit[b], Hasmet Ayhan Hanagasi[b], Sinem Kocagil[a], Beyhan Durak Aras[a], Oya Uyguner[e], Murat Emre[b]

[a] Department of Medical Genetics, Eskisehir Osmangazi University, Eskisehir, Turkey
[b] Department of Neurology, Istanbul University, Istanbul, Turkey
[c] Department of Neurology, Istanbul Atlas University Faculty of Medicine, Istanbul, Turkey
[d] Vocational School Health Services, Oral and Dental Health, Altınbas University, Istanbul, Turkey
[e] Department of Medical Genetics, Istanbul University, Istanbul, Turkey

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ABSTRACT

Just as its clinical heterogeneity, genetic basis of Frontotemporal dementia (FTD) is also diverse and multiple molecular pathways are thought to be involved in disease pathogenesis. In the present study, FTD-related genes were evaluated in a Turkish cohort of 175 index FTD patients with a gene panel including *GRN, MAPT, TARDBP, FUS, CHMP2B* and *VCP* genes. Potential genetic associations were prospected in 16 patients (9.1%); five variants (p.(Gly35Glufs) and p.(Cys253Ter) in *GRN*; p.(Arg95Cys) in *VCP*; p.(Met405Val) in *TARDBP* and p.(Pro636Leu) in *MAPT*) were classified as pathogenic (P) or likely pathogenic (LP), in four familial and one sporadic patients. Three novel variants in *MAPT, CHMP2B* and *FUS* were also identified in familial cases. The most common pathogenic variants were observed in the *GRN* gene with a frequency of 1.14% (2/175) and this rate was 4.57% (8/175), including variants of uncertain significance (VUS). In this study with the largest cohort of Turkish FTD patients, *GRN* and *MAPT* variants were identified as the most common genetic associations; and rare causes like *VCP, TARDBP, CHMP2B and FUS* variants are recommended to be considered in patients with compatible clinical findings.

1. Introduction

The term Frontotemporal dementia (FTD) defines a group of neurodegenerative disorders that are clinically, pathologically, and genetically heterogeneous. It accounts for 15-20% of all dementias, and constitutes the most common form of early-onset dementia in individuals younger than 60 years of age (Olszewska et al., 2016). The prevalence of FTD varies in different populations, ranging from 31/100.000 in Italy to 2/100.000 in Japan (Gilberti et al., 2012; Ikejima et al., 2009). In Turkey, there is only one study regarding the epidemiology of frontotemporal dementia prevalence and the estimated prevalence was 1.1% (Gurvit et al., 2008; Hogan et al., 2016).

Clinically FTD is characterized by progressively worsening deficits in behavior, social cognition, executive functions, language and motor function due to neurodegeneration of the frontal and temporal lobes (Olney et al., 2017). Although FTD displays a heterogeneous clinical picture, the disease can be separated into two main groups: behavioral variant FTD (bvFTD), the most common subgroup accounting for about 60% of FTD cases, and primary progressive aphasia (PPA) which is further differentiated into semantic variant PPA (svPPA) and nonfluent/agrammatic aphasia (nfvPPA) (Hogan et al., 2016; Onyike and Diehl-Schmid, 2013). There are also some other FTD related disorders in the spectrum, called FTD with motor neuron disease (FTD-MND), progressive supranuclear palsy syndrome (PSP-S), and corticobasal syndrome (CBS) (Olney et al., 2017). The early phases of these phenotypes have distinct clinical

* Corresponding author at: Department of Medical Genetics, Eskisehir Osmangazi University, Eskisehir, Turkey, Tel: +905397946467
E-mail address: ebruerzurumluoglu@gmail.com (E. Erzurumluoglu Gokalp).
# Both authors contributed equally to this manuscript as first author.

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features, however significant overlap may develop as disease progression (Rainero et al., 2017).

The complex clinical and pathological features of FTD reveal that genetic effect shows heterogeneity. Despite the efforts to elicit FTD genetics for more than 20 years, the basic molecular mechanisms of phenotypic and pathological traits have not been completely clarified yet. However, thanks to the technological advances in the last decade, the molecular pathophysiology of FTD and many other complex disorders are being enlightened. A large number of genes have been found to be directly causing or increasing susceptibility to the disease. Linkage analysis, whole-exome sequencing (WES), and genome-wide association studies (GWAS) have identified many genetics factors associated with familial/sporadic FTD and FTD-ALS. Hitherto, more than twenty genes have been linked to FTD development (Sellami et al., 2020).

Mutations in the progranulin (*GRN*) (Baker et al., 2006; Gijselinck et al., 2008), chromosome 9 open reading frame 72 (*C9orf72*) (DeJesus-Hernandez et al., 2011; Renton et al., 2011), and microtubule-associated protein tau (*MAPT*) (Hutton et al., 1998; Rainero et al., 2017) are the major causes of familial or sporadic FTD whereas mutations in the transactive response DNA binding protein (*TARDBP*) (Borroni et al., 2009), FUS RNA binding protein (*FUS*) (Mackenzie et al., 2010), charged multivesicular body protein 2B (*CHMP2B*) (van der Zee et al., 2007), valosin containing protein (*VCP*) (Watts et al., 2004) and TANK binding kinase1 (*TBK1*) (Pottier et al., 2015) genes are rare causes. Genetic modifiers such as *TMEM106B, RAB38*, and *CTSC* have been found to affect the penetrance, age of onset and clinical severity of the disease (Sirkis et al., 2019). *MAPT, GRN*, and *C9orf72* variants are responsible for 3-14%, 1-16% and 12-29% of FTD in western countries, respectively, however lower frequencies were reported in Asian populations. The difference is especially significant in the prevalence of pathogenic *C9orf72* hexanucleotide expansions. The carrier rate is markedly high in Europe compared to large Asian cohorts (<1%). We previously emphasized that the prevalence of *C9orf72* G4C2 expansions in FTD cases is lower (1%) compared to the West but higher than the Asian populations in our cohort (Aswathy et al., 2014; Erzurumluoglu et al., 2019; Kim et al., 2014; Ogaki et al., 2013).

In this study, we aimed to determine the frequencies of *GRN, MAPT, TARDBP, FUS, CHMP2B, VCP* gene variants associated with FTD in a large Turkish cohort and to evaluate the genotype/phenotype correlations.

2. Methods

2.1. Subjects

The study was conducted according to the Declaration of Helsinki guidelines and approved by the Clinical Practice Ethics Committee of Eskisehir Osmangazi University, Medical Faculty (2014/12). Biological samples were collected after obtaining written informed consent. One hundred and seventy-five index patients, 98 women and 77 men, diagnosed with FTD by detailed clinical and neuropsychological examination were included into the study. Mean age at diagnosis and age of symptom onset were 60.20 ± 8.8 and 55.75 ± 9.05 years, respectively. Patients were recruited from neurology outpatient clinics of Eskisehir Osmangazi University, Acibadem Hospital and İstanbul University, Istanbul Faculty of Medicine, Behavioral Neurology and Movement Disorders Unit. All patients had one of the FTD associated-clinical phenotypes with bvFTD, svPPA, nfvPPA, FTD-MND, PSP-S and CBS. Clinical diagnoses were made in accordance with the appropriate clinical diagnostic criteria. One hundred age-matched individuals with no clinical manifestations of neurodegenerative diseases and no positive family history of dementia, were included as control group. All control subjects had Mini-Mental State Examination (MMSE) above 26/30, indicative of no cognitive impairment. Mean age in the control group (60 women, 40 men) was 58.30 ± 9.1 years. Both of the patients and the controls were originated from Turkey.

2.2. Genetic analyses

Genomic DNA was isolated from peripheral blood samples by using Magna Pure Compact LC (Roche Applied), according to the recommendations of the manufacturer. 175 patients with FTD and all control individuals were screened for the *C9orf72* G4C2 repeats expansion by fragment length analysis (DeJesus-Hernandez et al., 2011) and repeat-primed polymerase chain reaction (Renton et al., 2011), as described previously. Our data of *C9orf72* G4C2 expansion in a hundred FTD patients has been published before. We have detected *C9orf72* G4C2 expansions in one FTD patient (1%) (Erzurumluoglu et al., 2019). No pathogenic *C9orf72* repeat expansion was revealed in the remaining patients (n = 76) and then, all were included into next-generation sequencing analyses of frequently seen FTD-related gene variants.

A panel consisting of *MAPT, GRN, CHMP2B, VCP, TARDBP* and *FUS* genes was designed using ION Ampliseq Disagner software. These amplicons were optimized by Thermofisher Scientific. The target region was enriched using Ion AmpliSeq Library Kit v.2.0 (Thermo Fisher Scientific). The exons and exon-intron junctions for related genes were sequenced in both patients and controls by using Ion-Torrent S5 (Thermo Fisher Scientific), according to the protocol of the manufacturer.

2.3. Next-generation sequencing variant analyses

Sequence reads were aligned to reference genome (GRCh37/hg19) using the Ion Torrent platform-specific pipeline software Torrent Suite 4.2. The Ion Reporter 4.0 (Thermo Fisher Scientific), Integrative Genomics Viewer (IGV) and Varsome (http://www.varsome.com) (Kopanos et al., 2019) softwares were used to analyse the data. Variants with a minor allele frequency (MAF) higher than 0.1% in Genome Aggregation Database (http://gnomad.broadinstitute.org/) were filtered out. MutationTaster (http://www.mutationtaster.org/), Prediction of effects of human nsSNPs (http://genetics.bwh.harvard.edu/pph2/), Scale-invariant feature transform (http://sift.jcvi.org/) were used to evaluate the effect of nonsynonymous variants on protein function and structure, Human Splicing Finder (http://www.umd.be/HSF/) /) was used to predict the effect of mutations on splicing. We interpreted the identified variants using the Alzheimer Disease & Frontotemporal Dementia Mutation Database (www.molgen.ua.ac.be/admutations/) (Cruts et al., 2012), The Human Gene Mutation Database (http://www.hgmd.cf.ac.uk/ac/), ClinVar (http://www.ncbi.nlm.nih.gov/clinvar/) and literature search. Nucleotide changes were numbered corresponding to NM_001123066.3 (*MAPT*), NM_002087.2 (*GRN*), NM_014043.3 (*CHMP2B*), NM_007126.3 *(VCP)*, NM_007375.3 (*TARDBP*) and NM_001170937.1 (*FUS*) transcripts. Variants were named according to HGVS Human Genome Variation Society (http://www.hgvs.org) nomenclature and classified according to the American College of Medical Genetics and Genomics guidelines for the interpretation of sequence variants (ACMG) (Richards et al., 2015). Direct sequencing by capillary electrophoresis (3130xl Genetic Analyzer, Applied Biosystems) was performed for the confirmation of detected mutations that have been linked with familial history and clinical data.

Table 1
Clinical and demographic features of patients and controls

	FTD cohort	Control cohort	p-value
N	175	100	
Gender (female/male)	98/77	60/40	0.519[a]
Age	60.20 ± 8.8	58.30 ± 9.1	0.090[b]
Age at onset	55.75 ± 9.05	-	
Clinical phenotype	Total	Positive family history	
bvFTD	123	48	
nfvPPA	18	10	
svPPA	15	10	
FTD-MND	10	8	
CBS	7	2	
PSP-like S	2	-	
Total	175	78	

FTD: Frontotemporal dementia; *bvFTD:* behavioral variant frontotemporal dementia; *svPPA:* Semantic variant primary progressive aphasia; *nfvPPA:* Nonfluent-agrammatic variant primary progressive aphasia; *FTD-MND:* frontotemporal dementia with motor neuron disease; *CBS:* Corticobasal syndrome; *PSP-like S:* Progressive supranuclear palsy like syndrome.
[a] *p = Level of significance according to the χ^2test*
[b] *p= Level of significance according to student t-test*

2.4. Statistical analysis

Statistical analysis was performed using the Statistical Package of the Social Sciences (SPSS) 21.0 (IBM, NY, USA). Qualitative variables were given as frequency and percentage, whereas quantitative variables were shown as mean ± standard deviation. Normality of age values across the groups was evaulated with Shapiro Wilk test. Student t test was used to compare age values of FTD and control groups. Homogenity of sex distribution in FTD and control cohorts was evaluated with χ^2 analysis. Statistically significant evidence of association was determined by p-values of 0.05 or below.

3. Results

3.1. Demographic and clinical characteristics of the study groups

Distribution of clinical phenotypes was as following: 123 patients had bvFTD, 18 nfvPPA, 15 svPPA, 10 FTD-MND, 7 CBS and 2 PSP-like S were present. Of these patients, 78 (44.5%) had a positive family history of dementia in the first-degree relatives. Gender and age distributions were not statistically different between FTD and control groups (p> 0.05). Clinical and demographic characteristics of patients and controls are given in Table 1.

3.2. Results of genetic analyses and clinical findings

Genetic screening for FTD-related genes was performed in 175 patients without pathogenic *C9orf72* G4C2 expansion. Overall, we identified a total of 16 patients carried 17 variants and four of them were classified as pathogenic (P), one was likely pathogenic (LP) while 12 were interpreted as variant of unknown significance (VUS) (16/175, 9.14%). None of these variants were detected in our control group. Three P, one LP and eight VUS variants were detected in patients with a positive family history, and the prevelance was 14.10% (11/78). One patient had two variants which were classified as P and VUS. The variant frequency was calculated through the number of cases (Fig. 1).

Three novel variants were identified in the *MAPT* c.1828-3A>C, *CHMP2B* p.(Lys130Arg), and *FUS* p.(Tyr17=) genes and all of them were classified as VUS.

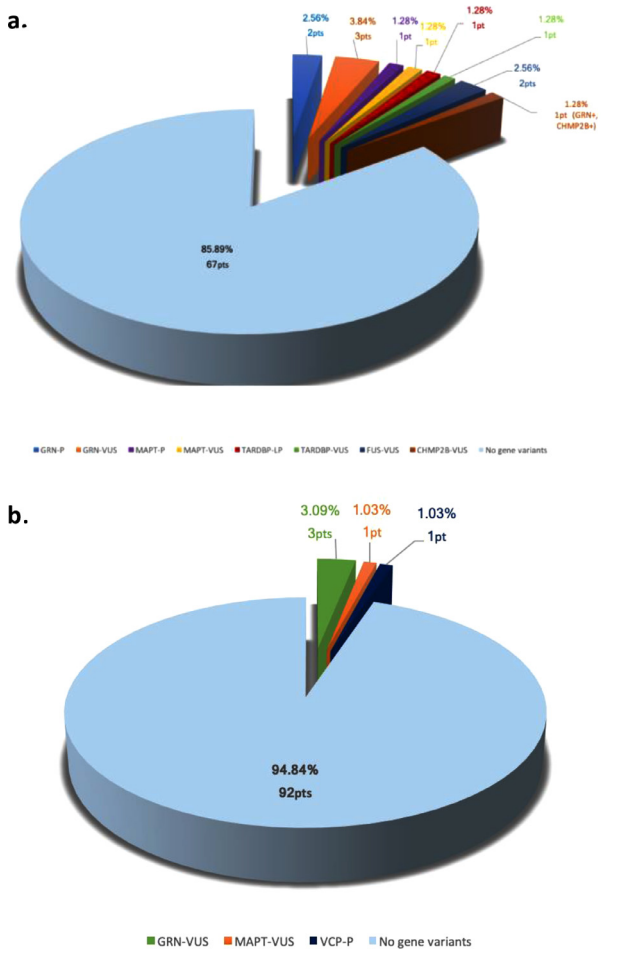

Fig. 1. Frequency of variants in **a.** cases with positive, **b.** cases with negative family history of dementia. pts: patients

3.2.1. Pathogenic and likely pathogenic variants

The most common pathogenic variants were observed in the *GRN* gene with a frequency of 1.14% (2/175), the rate was 2.56% (2/78) in patients with a positive family history of dementia. p.(Gly35Glufs) variant of *GRN* was detected in the bvFTD patient (I14). This variant has previously been reported as pathogenic. The symptoms of the patient I14 started at the age of 57 with memory impairment. He developed disinhibition, aggressive behaviour, stereotypical movements, and parkinsonism within two years. Magnetic resonance imaging (MRI) showed global atrophy of the brain, prominent in bilateral hippocampus and parietal cortices, and mild periventricular white matter abnormalities.

The other pathogenic *GRN* variant, p.(Cys253Ter) was detected with the co-occurrence of a novel *CHMP2B* p.(Lys130Arg) (described below) in bvFTD patient (P61) (Fig. 2). The symptoms of this patient started at the age of 56 with amnesia, aggressive behaviour, self-neglect, failure to achieve daily routines, stereotypical movements and she developed unilateral hemiparesis during the disease course.

A common pathogenic mutation in exon 10 of *MAPT*, p.(Pro636Leu), was identified in patient IR1, whose first symptoms were personality changes such as social withdrawal, disinhibition, inappropriate affect, and hyperphagia and was diagnosed with bvFTD at the age of 51. She developed subsequent aphasia, mutism, and parkinsonism during the follow-up. Brain MRI of her showed atrophy of the frontotemporal cortices, bilateral hippocam-

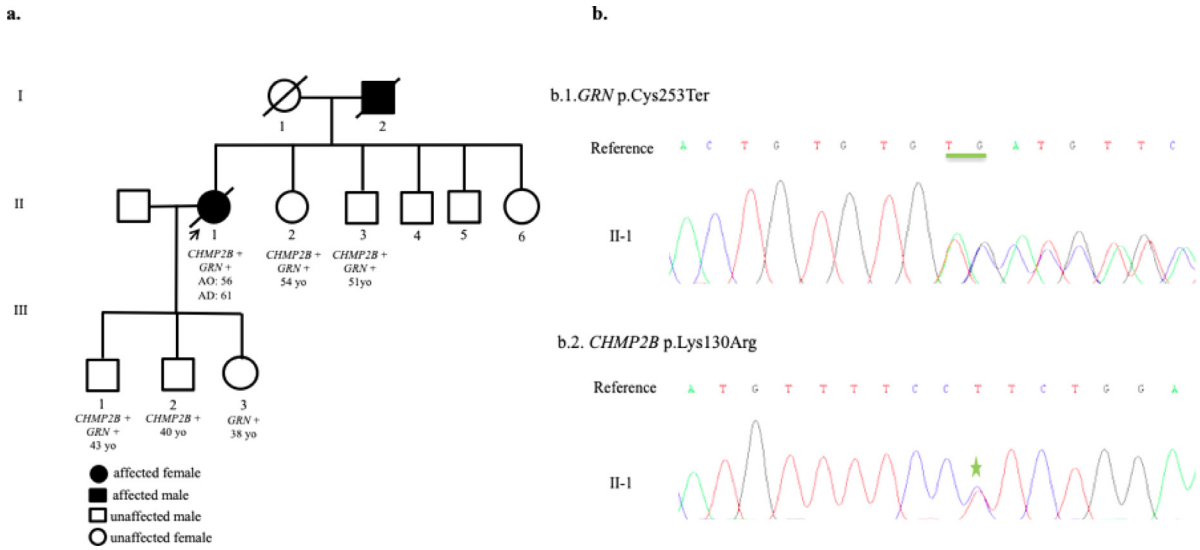

Fig. 2. a. Pedigree of the P61. The index case is marked with the arrow. AO: age at disease onset, AD: age of death, yo: years old. **b.** Sanger Sequencing of the patient II-1 showing both the b.1. *GRN* p.(Cys253Ter) and b.2. *CHMP2B* p.(Lys130Arg). The green asterisk and line mark show mutation regions.

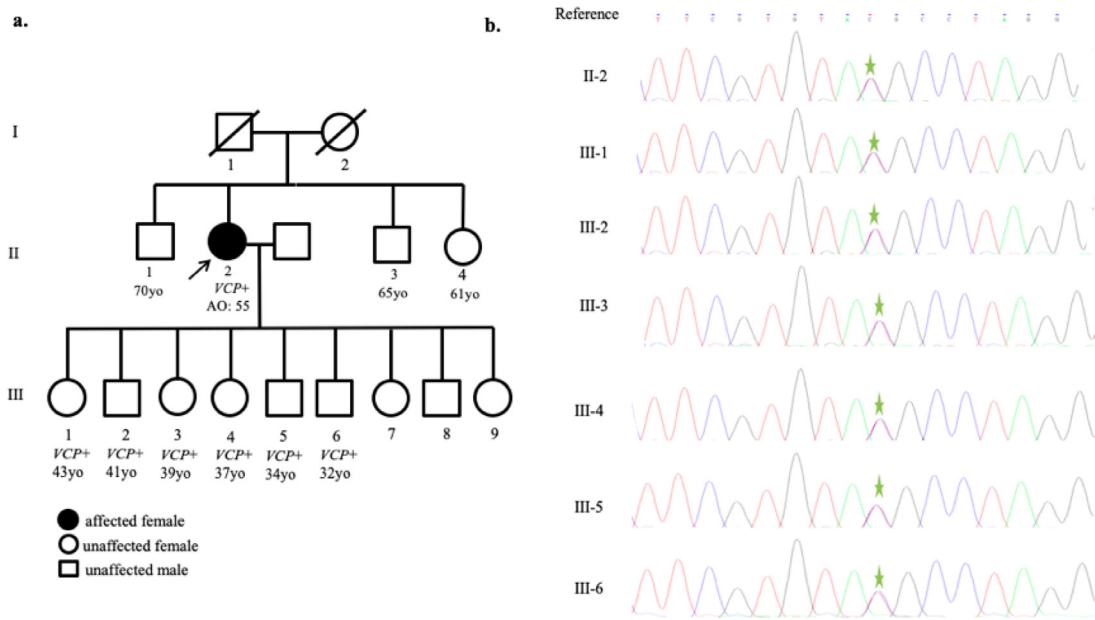

Fig. 3. a. Pedigree of the AC6. The index case is marked with the arrow. AO: age at disease onset, yo: years old. **b.** Sanger Sequencing of the patient II-2 and her six children showing the *VCP* p.(Arg95Cys). The green asterisks show mutation regions.

pus and anterior part of the corpus callosum, and mild ventricular enlargement.

The *VCP* variant, p.(Arg95Cys), was identified in a bvFTD patient (AC6). The first symptom of the patient was memory impairment at the age of 55, echolalia and psychotic symptoms developed subsequently. Brain MRI revealed frontal lobe atrophy. Electromyography was compatible with myopathy. But no muscle biopsy could be performed to confirm the diagnosis of inclusion body myopathy because the patient did not accept it. Segregation analysis showed inheritance of this variant in six of her nine asymptomatic children who were <45 years old (Fig. 3).

The likely pathogenic *TARDBP* variant, p.(Met405Val), seen in a FTD-MND case (P26) was grouped as likely pathogenic. The first symptom in this patient was amnesia appearing at the age of 70. In further course, he became disoriented with hypersexuality, overspending, overeating, and excessive sleeping. Later on, tremor and muscle weakness developed, primarily affecting his hands. MRI showed frontotemporal atrophy which was more prominent in the left side. His mother and the two brothers were also suffered from the similar symptoms. Unfortunately, segregation analysis could not be performed in this family (Fig. 4).

The detected pathogenic and likely pathogenic variants and corresponding clinical findings are summarized in Table 2.

3.2.2. Rare variants of Unknown Significance

A total of six variants of unknown significance of *GRN* gene were found including four missense (p.Cys150Arg, p.Cys139Arg,

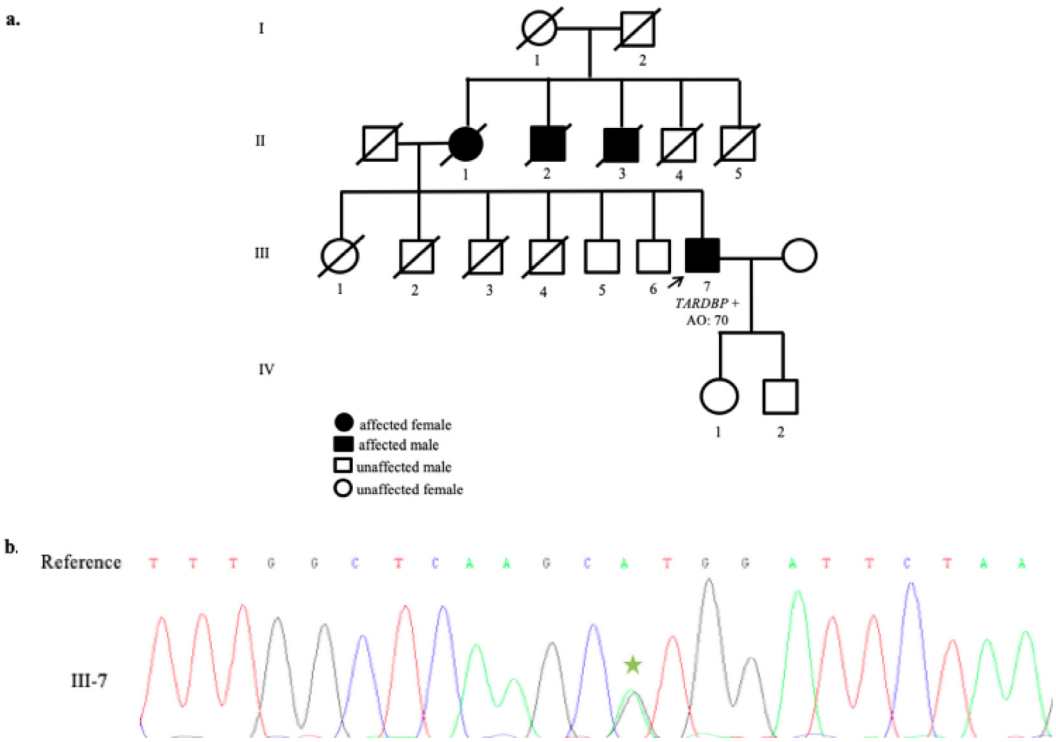

Fig. 4. a. Pedigree of the P26. The index case is marked with the arrow. AO: age at disease onset. **b.** Sanger Sequencing of the patient III-7 showing the *TARDBP* p.(Met405Val). The green asterisk shows mutation region.

p.Val90Met, p.Asp144Asn), one intronic (c.933+8delG) and one non-frameshift deletion p.(Asn119del) in our study.

Patient I30, carrying the p.(Cys150Arg) variant of *GRN*, was initially presented with tremor affecting the upper extremities and bradykinesia at the age of 59, and developed memory deficit, social withdrawal within three years. His brain MRI was compatible with bilateral dorsolateral prefrontal atrophy, more prominent on the right, as well as mild parietal atrophy.

GRN p.(Cys139Arg) variant was detected in a bvFTD patient (G1). The symptoms started with suspiciousness and social withdrawal at the age of 55. Subsequently echolalia, memory loss, paranoia, impaired executive functions and somatic symptoms were developed with reduced facial expressions, bradykinesia, and apraxia. Brain MRI showed global atrophy of the brain predominantly in the frontoparietal areas which was more prominent in the left side. His father suffered from similar symptoms but his DNA was not available. Segregation analysis revealed his 52-year-old asymptomatic son was also carrying the same variant (Fig. 5).

Patient G2, diagnosed with bvFTD, had GRN p.(Val90Met) variant. The patient, who had also suffered from two hemorrhagic cerebrovascular events 15 and 11 years ago and had right-sided hemiparesis, started having progressive gait disturbance, bradykinesia and memory impairment along with irritability at the age of 67. He had paranoias that people are stealing from him. He became dependent in self-care within one year. The brain MRI revealed left occipital encephalomalacia and bilateral hippocampal, anterior temporal and parietal atrophy more prominent on the right side.

GRN p.(Asp144Asn) variant was detected in svPPA (G3) who had a positive family history of dementia. Memory deficit and aphasia were started at the age of 59. Temporal atrophy predominantly in the left side was seen in the brain MRI.

Patient (G4) diagnosed with sporadic bvFTD had GRN c.933 + 8delG. Symptoms including agitation, aggression and memory deficit were started at age of 58.

Symptoms of proband (G5) started with anxiety, obsession, impairment of episodic memory when she was 58 years old. Her brain MRI showed mild hippocampal atrophy and structural changes in white matter. The father and aunt of this case were diagnosed with dementia. *GRN* p.(Asn119del) was detected in this patient but segregation analysis could not be performed

We identified two *MAPT* VUS variants. One of them was as a novel variant c.1828-3A>C defined in the svFTD patient (M1) with positive family history. Single-word comprehension deficit, visuospatial memory deficit, prosopagnosia, and apathy started at the age of 40 in this case. MRI showed marked anterior temporal lobe atrophy more prominent on the right side. The *MAPT* c.1828-3A>C variant is located near canonical sites in intron 11 and may result in activation of a cryptic acceptor site and thus predicted to affect alternative splicing according to Human Splicing Finder tool. Nevertheless, this novel variant was classified as VUS since there was no other evidence suggesting its pathogenicity. Second *MAPT* variant was (p.Glu320del) that located in exon 6 and, was detected in the sporadic bvFTD patient (M2). Brain MRI of the case showed frontotemporal atrophy.

The novel *CHMP2B* p.(Lys130Arg) variant that has not been defined before was identified in the bvFTD patient P61 in which the above-mentioned pathogenic *GRN* p.(Cys253Ter) variant was also detected. *CHMP2B* p.(Lys130Arg) variant is located in a highly conserved nucleotide residue (phyloP: 4.81) and classified as "possibly damaging", "tolerated", and "disease-causing" by PolyPhen-2, SIFT, and MutationTaster, respectively. Segregation analysis revealed that co-occurrence of these two variants were present in both the 54-year-old sister and 51-year-old brother of the index case. In addition, it was observed that her daughter had only the *GRN* variant, while one of her sons had in both variants and only the CHMP2B variant in the other son (Fig. 2). All these family members were asymptomatic as of yet.

Table 2
Clinical features of patients carrying pathogenic or likely pathogenic variants

CaseNo.	*Genes*	*cDNArs ID*	*Protein*	*In-silico prediction*	*MAF%*	*ACMG Class*	*Clinical findings*	*CP*	*AO*	*FH*
IR1	*MAPT*	c.1907C>T rs63751273	p.(Pro636Leu)	PD/Del/DC	0.0005353	P	Social withdrawal, hyperphagia, disinhibition, inappropriate affect, word-finding difficulty, mutism, parkinsonism	bvFTD	51	+
I14	*GRN*	c.102delC rs63751073	p.(Gly35Glufs)	na/na/DC	0.00319	P	Memory problems, disinhibition, aggressive behavior, stereotypical movements, parkinsonism	bvFTD	57	+
P61	*GRN*	c.759_760delTG rs63751035	p.(Cys253Ter)	na/na/DC	0.0004	P	Amnesia, aggressive behavior, self-neglect, failure to achieve daily routines, stereotypical movements, unilateral hemiparesis	bvFTD	56	+
AC6	*VCP*	c.283C>T rs121909332	p.(Arg95Cys)	B/Del/DC	0.000398	P	Memory problems, echolalia, psychotic symptoms, myopathy	bvFTD	55	-
P26	*TARDBP*	c.1213A>G rs762209110	p.(Met405Val)	PD/Tol/DC	0.0004	LP	Amnesia, hypersexualized, overspending, overeating and oversleeping, tremor and muscle weakness	FTD-MND	70	+

In silico prediction: PolyPhen-2, SIFT, Mutation Tester, respectively
Polyphen predictions: B-Benign, PD- Possibly Damaging, PbD- Probably Damaging, SIFT predictions: Del- Deleterious, Tol- Tolerated.
Mutation Tester predictions: DC- Disease-causing, Poly- polymorphism, na: not available
MAF: Minor allele frequency from gnomAD (The Genome Aggregation Database), CP: clinical phenotype, AO: age at disease onset, FH: family history
MAPT (NM_001123066.3), *GRN* (NM_002087.2), *VCP* (NM_007126.3), *TARDBP* (NM_007375.3), *CHMP2B* (NM_014043.3), *FUS* (NM_001170937.1).

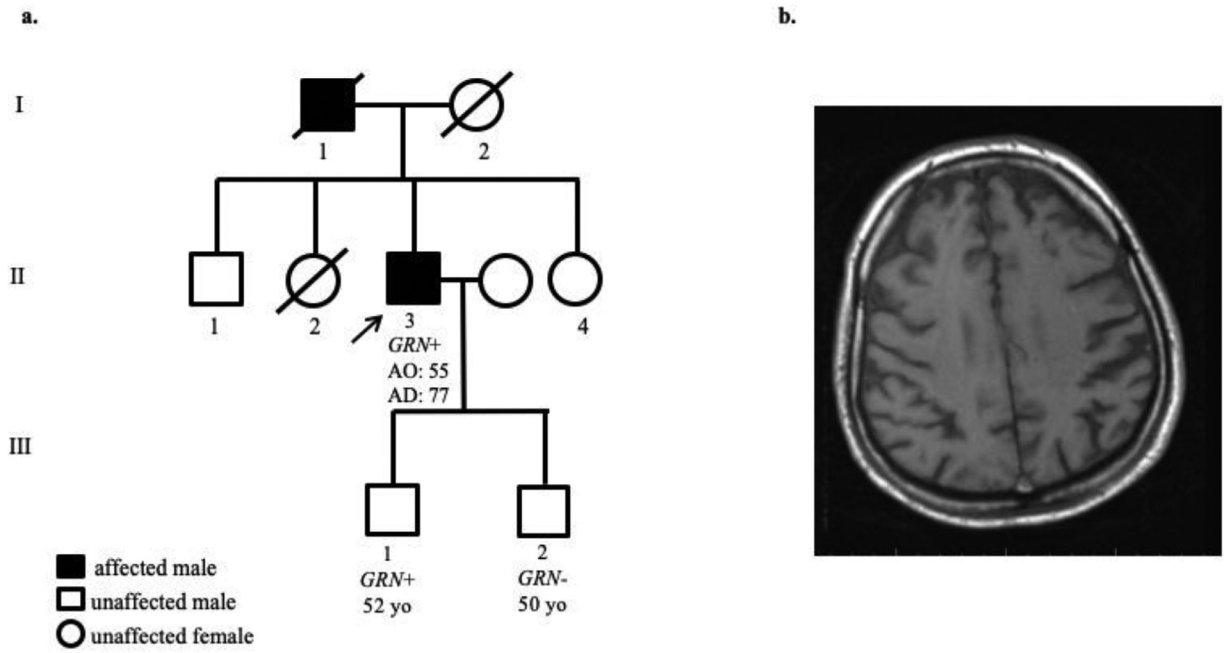

Fig. 5. a. Pedigree of the G1. **b.** Brain MRI of the patient II-3 show global atrophy of the brain predominantly in the frontoparietal areas which was more prominent in the left side.

TARDBP p.(Ser292del) variant was detected in a familial FTD case (T1). The symptoms of the patient started with memory deficit at the age of 63, and behavioral changes were added in a short time. Her mother and sister also have been diagnosed with dementia. MRI showed bilateral perisylvian, hippocampal and parietal atrophy, more prominent on the left side.

The patient (F1) with FTD-MND had the novel variation p.(Tyr17 =) located at the end of the 3rd exon of the *FUS* gene. This variant was a synonymous that does not cause any amino acid changes in the protein and was not found in Genome Aggregation Database. However, there is a possibility that this variant may affect the splicing process through altering the ESE (exonic splicing enhancer) region according to the Human Splicing Finder tool. Patient (F1) has showed episodic memory impairment starting at the age of 52 and later developed mild motor impairment.

We also identified previously reported in-frame deletion of *FUS* p.(Gly144_Tyr149del), in a patient with svPPA. The first significant symptoms of the patient were memory impairment and reduced

Table 3
Variations classified as VUS in this study

CaseNo.	*Genes*	*cDNArs ID*	*Protein*	*In-silico prediction*	*MAF%*	*CP*	*AO*	*FH*
I30	*GRN*	c.448T>C rs772101308	p.(Cys150Arg)	PbD/Del/DC	0.000398	bvFTD	59	-
G1	*GRN*	c.415T>C rs763841075	p.(Cys139Arg)	PbD/Del/DC	0.0179	bvFTD	55	+
G2	*GRN*	c.268G>A rs200019356	p.(Val90Met)	Tol/B/Poly	0.0119	bvFTD	67	-
G3	*GRN*	c.430G>A rs200591137	p.(Asp144Asn)	PbD/Tol/DC	0.000795	svPPA	59	+
G4	*GRN*	c.933+8delG rs766099642	p.?	-	0.00239	bvFTD	58	-
G5	*GRN*	c.355_357delAAC rs758168578	p.(Asn119del)	na/na/Poly	0.00398	bvFTD	58	+
P61	*CHMP2B*	c.389A>G Novel	p.(Lys130Arg)	PD/Tol/DC	NA	bvFTD	56	+
M1	*MAPT*	c.1828-3A>C Novel	p.?	-	NA	svFTD	40	+
M2	*MAPT*	c.958_960delGGA rs760190465	p.(Glu320del)	na/na/Poly	0.00239	bvFTD	65	-
T1	*TARDBP*	c.876_878delCAG rs747244376	p.(Ser292del)	na/na/DC	0.000796	bvFTD	63	+
F1	*FUS*	c.430_447del rs747579808	p.(Gly144_Tyr149del)	na/na/DC	0.00795	svPPA	43	+
F2	*FUS*	c.51C>T Novel	p.(Tyr17=)	-	NA	FTD-MND	52	+

?= unknown effect
In silico prediction: PolyPhen-2, SIFT, Mutation Tester, respectively
Polyphen predictions: PD- Possibly Damaging, PbD- Probably Damaging, SIFT predictions: Del- Deleterious, Tol- Tolerated,
Mutation Tester predictions: DC- Disease-causing, Poly- polymorphism, na: not available
MAF: Minor allele frequency from gnomAD (The Genome Aggregation Database), CP: clinical phenotype, AO: age at disease onset, FH: family history
MAPT (NM_001123066.3), *GRN* (NM_002087.2), *VCP* (NM_007126.3), *TARDBP* (NM_007375.3), *CHMP2B* (NM_014043.3), *FUS* (NM_001170937.1).

personal care at the age of 43. The demantia was severely progressive and loss of insight, difficulty in abstract thinking, lack of executive functions, apraxia, attention deficit, aggression, erotomania, myoclonic jerks in lower extremity devoloped. Frontotemporal and parietal atrophy more prominent in left side were seen in MRI. It is learned that her parent suffered from the similar symptomes. Neuropsychological tests revealed prevalent deterioration in all areas. The MMSE score was 11 and serious semantic flaws were observed. Segregation could not be tested in this family. The identified all VUS are given in Table 3.

4. Discussion

The present study was aimed to determine the frequency of *MAPT, PGRN, CHMP2B, VCP, TARDBP, FUS* variants in 175 familial or sporadic FTD patients, and to analyze genotype/phenotype correlations. To our knowledge, this study assessed the largest cohort of patients with FTD from Turkey.

MAPT is the first gene identified in familial FTD patients and encodes microtubule-associated protein tau (Hutton et al., 1998; Poorkaj et al., 1998). Pathogenic variants of *MAPT* allow tau to form toxic aggregates and disrupt cytoskeletal stability. The frequency of *MAPT* variants varies widely, with a rate of 0-3% in sporadic and 5-20% in familial FTD cases (Benussi et al., 2015). The rate is higher in Western populations than in Asians (He et al., 2018). The frequencies in the Brazilian, Swedish, and French FTD spectrum were 7.1%, 0.8%, and 3.2%, respectively (Le Ber et al., 2013; Takada et al., 2016; Öijerstedt et al., 2019). Despite the absence of pathogenic *MAPT* variants in Indian dementia and Korean FTD patients (Aswathy et al., 2014; Kim et al., 2014), a high frequency of *MAPT* variants has been reported in Japanese and Chinese FTD cohorts (Ogaki et al., 2013; Tang et al., 2016). In a previous study in a Turkish dementia cohort, the frequency of pathogenic variants of *MAPT* was 0.95% (1/105) in the total and 3.6% (1/28) in the FTD cohort (Guven et al., 2016). In our study, the prevalance of *MAPT* variants (one P, two VUS) in the total FTD population was 1.71%, while it was 2.56% in familial cases. Although the *MAPT* variants detected in our relatively large FTD cohort is within the reported ranges, the rate in cases with a positive family history is lower than previous reports.

The c.1907C>T p.(Pro636Leu) is one of the most common variations in the *MAPT* gene and is associated with 4R tauopathy (Palencia-Madrid et al., 2019). p.(Pro636Leu) shows inter and intrafamilial clinicopathologic heterogeneity While many cases carrying this variant have bvFTD and parkinsonism, some patients diagnosed with svFTD and Alzheimer's disease have also been reported. The mean age of symptom onset was reported as 51 (43–69) and 49 years (42–56) in two different study (Borrego-Écija et al., 2017; Tacik et al., 2017). The most common clinical presentation with a mutation in the *MAPT* is known to be bvFTD, in which parkinsonism and/or aphasia may develop over time. In our study, patient IR1 diagnosed with bvFTD at the age of 51 who had p.(Pro636Leu) variant in the *MAPT* gene, clinical findings of our patient were consistent with the previously described phenotypes.

GRN is the second gene associated with FTD, approximately 5-20% familial and 1-5% sporadic FTD patients have pathogenic variants of this gene (Ferrari et al., 2013). Mutation frequency varies significantly depending on the ancestry of the population. The prevalance of pathogenic *GRN* variants is 0-1.9% (Das et al., 2013; Kim et al., 2014; Ogaki et al., 2013; Tang et al., 2016) in Asian populations vs. 3-15% in North American and European populations. (Benussi et al., 2010; Öijerstedt et al., 2019) In our study, *GRN* gene variants were the most common genetic cause of FTD, with a frequency of 4.57% (8/175). Among familial cases, the P/LP variant frequency was 2.56%. This rate is lower than the range reported in North American and European studies. Nevertheless, in a population with a broad ethnic diversity as is the case in Turkey, a fre-

quency rate between frequencies detected in Asian and European populations is not surprising.

Haploinsufficiency of *GRN* causes ubiquitin-positive neuronal inclusions and leads to neurodegenerative disorders (Baker et al., 2006; Cruts et al., 2006). Although missense variants were also described, pathogenic *GRN* variants usually have a null effect and cause reduced progranulin expression. Most patients with *GRN* variants develop symptoms before the age of 75, mean age of onset is 60. The most common manifestations are apathetic behaviour, language dysfunction, and extrapyramidal signs (Van Mossevelde et al., 2018). In our study, two pathogenic frameshift variants were identified. In both cases, the age of onset was below age 60 (I14:57 yo and P61:56 yo), supporting an early age of onset in *GRN* mutation carriers.

The pathogenic *GRN* c.102delC p.(Gly35Glufs) was first identified in two patients with FTD (Gass et al., 2006) and in a Swedish family (Chiang et al., 2008). This mutation also detected in FTD patients with a variable clinical presentation in a large Swedish family. Initial symptoms were nonfluent aphasia, loss of speech, personality and behavioral changes, and rapid disease progression. Limb ataxia and parkinsonism were uncommon symptoms. Neuropathologically, severe frontal atrophy has been observed in affected members of the family (Skoglund et al., 2009). Although relative sparing of episodic memory is necessary for the diagnosis of FTD (Rascovsky et al., 2011), patients with mutations in *GRN* have been reported with pure memory impairment at the initial stage of the disease. Some of these cases developed impairment of executive functions later in the course, while some only had memory impairment up until the death (Kelley et al., 2009; Kelley et al., 2010; Le Ber et al., 2008). In our study, patient I14 was also found to carry this variant. His symptoms started at the age of 57 with memory impairment consistent with the literature. He developed typical bvFTD symptoms such as disinhibition, aggressive behaviour, stereotypical movements, and parkinsonism in two years. There was progressive white matter involvement and asymmetrical parietal atrophy in his MRI scan, and these findings are known to be associated with *GRN* mutation.

The *GRN* c.415T>C p.(Cys139Arg) variant is presumed to be likely pathogenic, it may lead protein misfolding by disrupting one of the cysteine disulfide bridges. Serum progranulin levels in p.(Cys139Arg) carriers were lower than in non-carriers (Piaceri et al., 2014; Rodríguez-Rodríguez et al., 2013). This mutation may also impair elastase-mediated cleavage and reduce neurite growth-stimulating activity (Wang et al., 2010). Redaelli et al. suggested that p.(Cys139Arg) may be associated with AD rather than FTD, based on neuropathological findings in two twin carriers (Redaelli et al., 2018). Steele et al. detected this variant in a patient with bvFTD and suggested that it may be a rare risk variant rather than a pathogenic variant (Steele et al., 2018). Guven et al. identified this variant in a Turkish patient with FTD at the age of 70 years (Guven et al., 2016). We also found this variant in another Turkish bvFTD patient. We have classified this variant as VUS according to ACMG criteria, but we believe that it may be a strong risk factor for FTD. Assessment of the neuropathological and clinical course in large cohorts of dementia carrying this variant will enable us to reach more precise conclusions about its pathogenicity.

CHMP2B mutations were reported to cause formation of aberrant endosomal structures (Skibinski et al., 2005). *CHMP2B* related FTD usually manifests between the ages of 46 and 65. Even though early symptoms are usually behavioral changes, some patients have progressive aphasia. Pyramidal and extrapyramidal signs may be observed later in the disease (Rainero et al., 2017). We found a novel variant in the *CHMP2B* gene c.389A>G p.(Lys130Arg) in one patient who also had a pathogenic *GRN* variant c.759_760delTG p.(Cys253Ter). p.(Cys253Ter) variant of *GRN* was initially reported in a patient with onset at age 58 and confirmed neuropathologically as FTLD-U (Gass et al., 2006). The second reported case was diagnosed as Lewy body dementia/bvFTD with loss of interest, loss of personal care, bulimia, stereotypic behavior, and disinhibition starting at the age of 61 (Le Ber et al., 2008). A third patient carrying p.(Cys253Ter) mutation was diagnosed with bvFTD at the age of 70 (Gómez-Tortosa et al., 2019). Our patient developed unilateral hemiparesis during the disease course. Pyramidal signs have not been reported in cases with p.(Cys253Ter) variant, hemiparesis can be related to the co-incident *CHMP2B* gene c.389A>G p.(Lys130Arg) variant. Since the disease progressed rapidly and the patient died within one year after the diagnosis, the coexistence of these variants is likely to result in poor prognosis and reduced survival. The interaction of various genetic factors may be a valuable prognostic marker.

Missense *VCP* variants were identified in inclusion body myopathy associated with Paget disease of bone and frontotemporal dementia (IBMPFD) (Watts et al., 2004). The gene encodes an AAA-ATPase protein superfamily responsible for many cellular processes, including membrane trafficking, organelle biogenesis, replication, ubiquitin-dependent protein degradation and protein folding (Weihl et al., 2005). Individuals with VCP-related FTD does not always have myopathy or Paget disease, they usually present with apathy, anomia, psychotic findings and nonspecific findings (Van Mossevelde et al., 2018). In 25-30% of patients with IBMPFD, FTD symptoms become apparent in early 50s. *VCP* mutations are observed in <1% of familial FTD cases (Sieben et al., 2012). In our study, the *VCP* c.283C>T p.(Arg95Cys) missense mutation was detected in one patient (0.57%). Although 80% of *VCP* mutation carriers have family history (Olszewska et al., 2016), there was no family history of dementia in our patient, however his father has died from myocardial infarction at an early age. The p.(Arg95Cys) mutation in the *VCP* gene was reported previously (Kimonis et al., 2008), in vitro functional studies showed a 3-fold increase in ATPase activity (Weihl et al., 2015). Different pathogenic variants detected in the same amino acid residue in IBMPFD patients were reported (Watts et al., 2004). Clinical features with myopathy accompanying dementia and slow disease progression in our patient was similar to other VCP mutation carriers.

TARDBP encodes TAR DNA binding protein 43, responsible for RNA regulation, and the protein is found to be a part of intraneuronal aggregates in FTD patients (Arai et al., 2006). Pathogenic variants of *TARDBP* are usually associated with ALS and have been found in <1% of FTD patients. Most of them are missense mutations affecting protein-protein interactions (Rainero et al., 2017; Sirkis et al., 2019). The frequency of pathogenic *TARDBP* variants in our cohort was 0.57% (1/175), consistent with other studies. We found c.1213A>G p.(Met405Val) variant that has not been associated with a clinical phenotype yet. This variant is located in exon 6, where almost all ALS-FTD missense mutations were identified (Prasad et al., 2019). This region is known to be associated with UBQLN2 in the C-terminal region, is likely to affect protein-protein interaction, which is essential for regulating TDP-43 levels (Cassel and Reitz, 2013). Therefore, we believe that this variant may be pathogenic, however, functional studies are needed to determine its pathogenicity.

The second *TARDBP* variant we found, c.874_876delAGC p.(Ser292del), is also located in exon 6, a hot spot region for *TARDBP* mutations. This deletion was classified as VUS based on the available evidence. The p.(Ser292del) variant was reported in two FTD siblings with C9orf72 expansion and one control case, its pathogenicity has not been elucidated due to the co-presence of hexanucleotide expansion. The possibility still exists that the control case could be presymptomatic as he was only 46 years

old (Kaivorinne et al., 2014). Cellular function of TDP-43 is regulated by phosphorylation (Gu et al., 2017), Ser292 is located in C-terminal region which is an important locus for phosphorylation, hence it may have a role in the regulation of TDP-43 protein. Kaivorinne et al. (2014) suggested that Ser292 is not involved in phosphorylation, while Nonaka et al., (2016) defined ser-292 as the phosphorylation site of aggregated TDP-43. Detection of AlSer292 (p.S292N) variant in three Chinese ALS patients (Xiong et al., 2010; Zou et al., 2012) supports that the notion that Ser292 residue may be important for neurodegeneration.

FUS encodes a DNA/RNA binding protein regulating various tasks including RNA splicing and DNA repair (Yamaguchi and Takanashi, 2016). Mutant proteins were identified in ALS for the first time in 2009 (Kwiatkowski et al., 2009) and were also detected in FTD cases later (Neumann et al., 2009). FUS related FTD usually starts earlier than other forms, before 40 years of age (Josephs et al., 2010). *FUS* gene inframe deletion p.(Gly144_Tyr149del) was detected in svFTD patient and similarly, the symptoms of our patient (F1) started at the age of 43. This deletion has been reported previously in patient carrying a diagnosis of inclusion body myositis with family history of ALS and also it was determined in one control sample (Brown et al., 2012). (Guven et al., 2016) and (Bartoletti-Stella et al., 2018) detected this variant in dementia patients. In addition to, missense p.Q140R mutation located in this deletion region of FUS were previously reported in ALS patient (Zou et al., 2020). Although p.(Gly144_Tyr149del) variant have a frequency of 0.00007953 in gnomAD, all individuals who had this variant were under 60 years old. Functional and segregation analysis were not yet available to confirm pathogenicity for this mutation. Even if this variant was classified as VUS based on the available data, we thought that this variant may likely to be pathogenic.

In conclusion, pathogenetic variants in *GRN, MAPT, VCP* and *TARDBP* genes were detected in Turkish FTD patients along with novel variants in *MAPT, CHMP2B, FUS*. The main limitation of our study is that segregation analyses could not be performed in all variant carriers. In our cohort 44,6% of patients had a positive family history. Based on the available information, the pattern of inheritance was autosomal dominant in the majority of patients. The frequency of pathogenic mutations was in the range of general frequency. Although *GRN* mutations have the highest frequency, we concluded that other rare gene variants should also be considered in FTD cases depending on their clinical features.

Author contribution

Sevilhan Artan: Project administration, Conceptualization, Methodology, Supervision, Writing-review & editing, Ebru *Erzurumluoglu Gokalp:* Conceptualization, Methodology, Formal analysis, Investigation, Visualization, Writing-original draft, review & editing, Bedia Samanci: Clinical diagnosis, Resources, Writing-review & editing, *Demet Ozbabalik Adapinar:* Clinical diagnosis, Resources, Writing - review & editing, *Hasan Bas:* Formal analysis, Validation, Writing - review & editing. Fatih Tepgec: Resources, Writing – review & editing. *Emilia Qomi Ekenel:* Formal analysis, Writing - review & editing. *Oguz Cilingir :* Resources, Validation, Writing - review & editing. *Basar Bilgic:* Clinical diagnosis, Resources, Writing – review & editing. *Hakan Gurvit:* Clinical diagnosis, Resources, Writing – review & editing. *Hasmet Ayhan Hanagasi:* Clinical diagnosis, Resources, Writing – review & editing. *Sinem Kocagil:* Validation, Writing - review & editing. *Beyhan Durak Aras:* Validation, Writing - review & editing. *Oya Uyguner:* Resources, Writing - review & editing. *Murat Emre:* Clinical diagnosis, Resources, Writing – review & editing

Disclosure

The authors declare no conflicts of interest. DNA samples were collected with the approval of the relevant institutional ethic boards and informed written consent was obtained from each participant.

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