

Progranulin Gene Mutations in Chinese Patients with Frontotemporal Dementia: A Case Report and Literature Review

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Abstract.

Background: Progranulin (*GRN*) mutations in frontotemporal dementia (FTD) have been less frequently reported in China than in Western countries.

Objective: This study reports a novel *GRN* mutation and summarizes the genetic and clinical features of patients with *GRN* mutations in China.

Methods: Comprehensive clinical, genetic, and neuroimaging examinations were conducted on a 58-year-old female patient diagnosed with semantic variant primary progressive aphasia. A literature review was also conducted and clinical and genetic features of patients with *GRN* mutations in China were summarized.

Results: Neuroimaging revealed marked lateral atrophy and hypometabolism in the left frontal, temporal, and parietal lobes. The patient was negative for pathologic amyloid and tau deposition by positron emission tomography. A novel heterozygous 45-bp deletion (c.1414-14.1444delCCCTTCCCCGCCAGGCTGTGTGCTGCGAGGATCGCCAGCACTGCT) was detected by whole-exome sequencing of the patient's genomic DNA. Nonsense-mediated mRNA decay was presumed to be involved in the degradation of the mutant gene transcript. The mutation was deemed pathogenic according to American College of Medical Genetics and Genomics criteria. The patient had a reduced plasma *GRN* level. In the literature, there were reports of 13 Chinese patients – mostly female – with *GRN* mutations; the prevalence was 1.2%–2.6% and patients mostly had early disease onset.

Conclusion: Our findings expand the mutation profile of *GRN* in China, which can aid the diagnosis and treatment of FTD.

Keywords: China, frontotemporal dementia, genetics, Progranulin (*GRN*)

INTRODUCTION

Frontotemporal dementia (FTD) is a spectrum of neurodegenerative disorders that includes behavioral variant FTD (bvFTD), progressive non-fluent aphasia, and semantic dementia [1]. The clinical and genetic features of FTD can overlap with those of neurodegenerative diseases including amy-

otrophic lateral sclerosis (ALS), Parkinson's disease (PD), cortical basal syndrome (CBS), and progressive supranuclear palsy (PSP) [2–4]. Approximately one-third of FTD cases harbor heritable pathogenic genes such as chromosome 9 open reading frame 72 (*C9orf72*), granulin (*GRN*), and microtubule-associated protein tau (*MAPT*) [5]. FTD caused by *GRN* mutations is rare in China compared with Western countries [5–8].

The *GRN* gene on chromosome 17q21 encodes progranulin (PGRN), a multifunctional 593-amino acid protein that promotes the development and survival of neurons and microglia [9]. Loss of PGRN function is a monogenic cause of FTD [10]. Approximately 114 pathogenic mutations in the *GRN* gene

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have been identified, including some that cause haploinsufficiency [8, 11]. *GRN* mutations that reduce the level of PGRN increase the risk of dementia, whereas increasing and/or restoring PGRN level is an effective therapeutic strategy [11]. Therefore, from the epidemiologic, clinical, and healthcare resource management standpoints, it is important to document the full spectrum of *GRN* mutations in China and their associated clinical manifestations.

In this study, we report a novel *GRN* mutation in a Chinese patient with FTD. We also summarize the genetic and clinical features of all Chinese patients with *GRN* mutations reported in the literature.

MATERIALS AND METHODS

Clinical and neuropsychological workup

The patient was evaluated at Xuanwu Hospital in Beijing, China. We collected a range of clinical data relating to initial symptoms, disease progression, and family history. A professional neurologist conducted neurologic testing. Cognitive function was assessed with the Mini-Mental State Examination (MMSE), Montreal Cognitive Assessment (MoCA). Disease severity was tested by Frontotemporal Lobar Degeneration-Clinical Dementia Rating scale (FTLD-CDR). Language function was evaluated with the Boston Naming Test (BNT). Behavioral abnormalities were assessed with the Frontal Behavior Inventory (FBI), and the ability to perform daily activities was evaluated with the Activities of Daily Living (ADL) scale.

The study was approved by the Ethics Committees of the Xuanwu Hospital of Capital Medical University, China, and was conducted according to the principles outlined in the Declaration of Helsinki. Written informed consent was obtained from the patient.

Neuroimaging

Positron emission tomography (PET) and magnetic resonance imaging (MRI) were performed at Xuanwu Hospital using a 3.0 T time-of-flight hybrid PET/MRI scanner (Signa PET/MR, GE Healthcare, Madison, WI, USA) with a 19-channel head and neck union coil. We also performed amyloid PET (AV45), tau PET (PI2620), and ^{18}F fluorodeoxyglucose (^{18}F -FDG)-PET. PET data were reconstructed using an ordered subset expectation maximization algorithm with weighted attenuation.

Whole-exome sequencing (WES)

The patient's genomic DNA (gDNA) was isolated from peripheral blood leukocytes (QIAamp DNA Blood Kits; Qiagen, Valencia, CA, USA). Her families refused genetic testing. We performed exome capture with a SureSelect Human All Exon V6+UTR (89 Mb) Kit (Agilent Technologies, Santa Clara, CA, USA). Paired-end sequencing was performed on a HiSeq2500 system (Illumina, San Diego, CA, USA) using HiSeq SBS Kit V4 (Illumina), which generated 100-bp reads. The average and minimum sequencing depths were $125\times$ and $20\times$, respectively. The following reference databases were used: hg38 (GRCh38) (<https://genome.ucsc.edu>), Human Gene Mutation Database (<https://www.hgmd.cf.ac.uk>), Genome Aggregation Database (gnomAD; <https://gnomad.broadinstitute.org>), ClinVar (<https://www.ncbi.nlm.nih.gov/clinvar/>), and Single Nucleotide Polymorphism Database (<https://www.ncbi.nlm.nih.gov/SNP>). WES data were analyzed for single-nucleotide variants and insertion/deletions in dementia-related genes (Supplementary Table 1). Minor allele frequency, conservation, predicted pathogenicity, and disease association were analyzed, and the results were confirmed by Sanger sequencing.

GRN gene sequencing

The gDNA sample of the patient was used for standard polymerase chain reaction (PCR) amplification of the deleted region flanking the intron 10/exon 11 boundary. All primers used in this study are listed in Supplementary Table 2. Amplification products were purified and sequenced in both directions. Sanger sequencing was performed by Eurofins Genomics (Louisville, KY, USA), and trace files were analyzed with Seq Scanner 2 software (Thermo Fisher Scientific, Waltham, MA, USA).

RNA isolation, reverse transcription, and quantitative real-time PCR (qRT-PCR)

Reverse transcription, Sanger sequencing, and qRT-PCR were performed using total RNA from blood samples of the proband and 3 wild-type control subjects. Total RNA was extracted from leukocytes using TRIzol reagent (Invitrogen, Carlsbad, CA, USA) according to the manufacturer's instructions. Reverse transcription was performed using the iScript gDNA Clear cDNA Synthesis Kit (Bio-

Rad, Hercules, CA, USA) and cDNA was amplified by long-range PCR using a primer set designed to amplify from the untranslated region (UTR) of exon 0 to exon 12 of *GRN*. qRT-PCR was performed with SoAdvanced Universal SYBR Green Supermix (Bio-Rad). Relative quantification of *GRN* gene expression levels was performed using the Δ CT method, with the level of the ribosomal protein S17 (*RPS17*) gene in leukocytes used for normalization.

Biomarker study and enzyme-linked immunosorbent assay (ELISA)

We analyzed PGRN expression levels in the patient carrying the Val473fs mutation, 5 FTD patients without *GRN* mutations, and 5 healthy control subjects. Plasma was obtained within 90 days from peripheral blood samples and was centrifuged, aliquoted, and stored within 2 h at -80°C until analysis. PGRN expression level in the samples was measured with the human Progranulin ELISA kit (Adipogen, Incheon, Seoul, Korea) according to the manufacturer's instructions using a 1:100 dilution of sample in $1\times$ diluent. Samples were added to the wells of a 96-well plate and incubated overnight at 4°C ; recombinant human PGRN provided with the ELISA kit was used as the standard. The wash solution was aspirated after each third wash to ensure that all residual wash solution was removed. This was followed by incubation with secondary antibody for 2 h at room temperature. The reaction substrate was then added, followed by a termination solution. Color intensity was measured at 450 nm within 10 min.

PGRN expression levels in FTD patients without *GRN* mutations and healthy controls subjects were compared with the Mann–Whitney U test. Results were considered statistically significant at $p \leq 0.05$.

Literature review

Two researchers (MC and HTN) performed a literature search in PubMed and EMBASE databases from inception to November 2022 for studies describing the clinical features and genotypes of patients with FTD in China. We included all patients who had been diagnosed with FTD and harbored *GRN* mutations. From each publication, we extracted the first author's name and year of publication as well as the patients' age of FTD onset, sex, family history, genotype, and phenotype.

RESULTS

Clinical and neuroimaging data

The patient was a 58-year-old woman with 14 years of education who used to work as a tour guide. At the age of 57 years, she underwent a change in personality, which manifested as a loss of interest in daily activities and a depressive state. One month later, she became apathetic and developed difficulty in finding words and in single-word comprehension; her speech output decreased, and she refused to communicate with her families or friends. She denied any history of drug use. The patient's pedigree is shown in Fig. 2A. Her mother had developed dementia at the age of 65 years and died at 70 years, but no other family member had a history of dementia, motor dysfunction, or neurodegenerative diseases. The patient's test scores were as follows: MMSE, 11; MoCA, 6; FTLD-CDR sum of the box, 6; BNT, 10; FBI, 19; and ADL, 25. We observed marked lateral atrophy (Fig. 1A) and hypometabolism (Fig. 1B) in the left cortex in the frontal, temporal, and parietal lobes by MRI and ^{18}F -FDG-PET.

Based on the patient's clinical and neuroimaging data, we considered a diagnosis of semantic variant primary progressive aphasia (svPPA) [12], which includes impaired naming, single-word comprehension, and object recognition for low-frequency items while repetition, grammar, and motor functions are spared. To exclude early-onset Alzheimer's disease (AD), we conducted amyloid (AV45; Fig. 1C) and tau (APN1607; Fig. 1D) PET scanning but found no evidence of pathologic protein deposition.

WES, GRN gene sequencing, and genetic analysis

We first carried out WES of gDNA from the patient. We examined gene mutations known to be involved in AD, FTD, or other dementia-related neurodegenerative diseases. We identified a heterozygous 45-bp deletion (c.1414-14.1444delCCCTTCCCCGCCAGGCTGTGTGCTGCGAGGATCGCCAGCACTGCT [GenBank accession no. NM_002087.3]) at the boundary between intron 10 and exon 11 of the *GRN* gene. There were no additional disease-causing mutations in any other genes.

We next examined the 45-bp deletion in the *GRN* gene in the patient; a fragment encompassing the deletion at the intron 10/exon 11 boundary of the

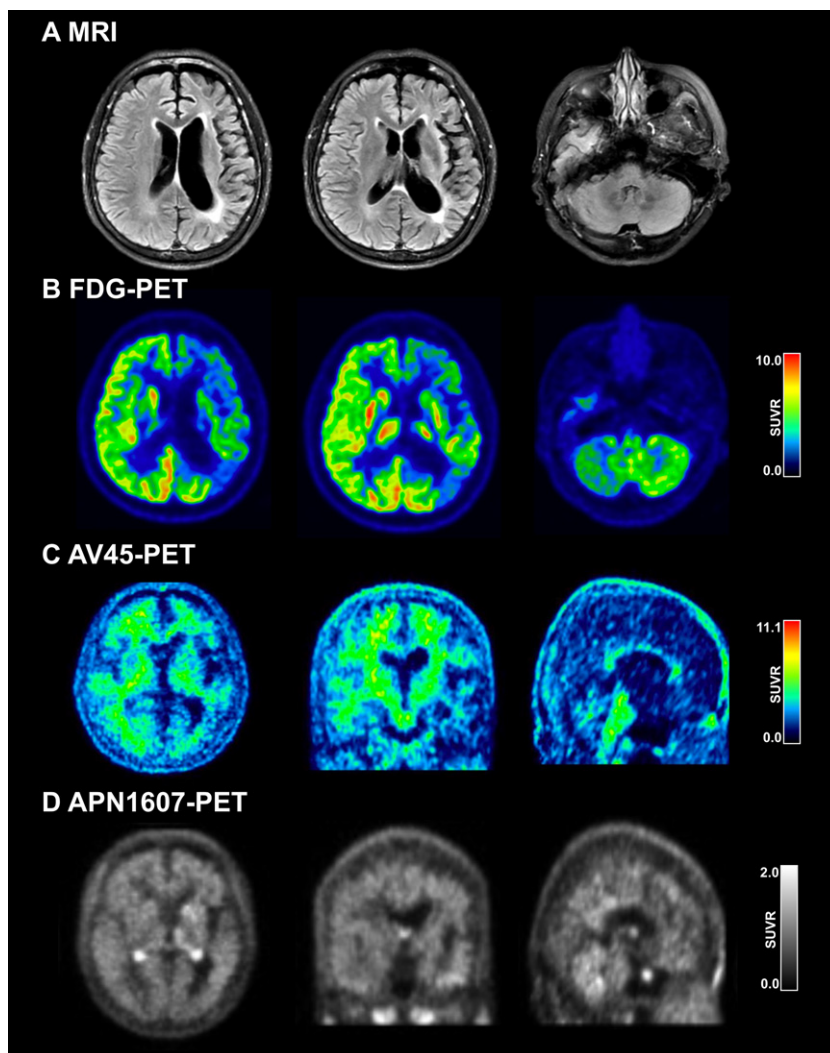


Fig. 1. Neuroimaging of the patient with *GRN* mutation. A) MRI showing left-side atrophy in the frontal, temporal, and parietal lobes. B) FDG-PET showing left-side hypometabolism in the frontal, temporal, and parietal lobes. C) AV45-PET showing absence of $A\beta$ deposition. D) APN1607 PET showing absence of tau deposition.

GRN gene was amplified by PCR. We examined PCR products from the patient and a wild-type control by agarose gel electrophoresis and Sanger sequencing. The results confirmed a heterozygous 45-bp deletion in the *GRN* gene in the proband (Fig. 2B, D).

The *GRN* deletion was absent from the HGMD, ClinVar, gnomAD, and 1000 Genomes databases (last access date of all databases: November 22, 2022). We, therefore, concluded that it was a novel causative mutation of FTD. Bioinformatic analyses using Mutation Taster (<https://www.mutationtaster.org>) predicted that this is a disease-causing mutation, and the mutation is pathogenic according to American

College of Medical Genetics and Genomics (ACMG) criteria (PVS1+PS3+PM2+PP3+PP4) [13].

Transcription analysis

The translation of gene transcripts can be disrupted by mutations in splicing elements or splicing signal sequences or by the introduction of premature termination codons (Supplementary Figure 1A) [14]. The 45-bp deletion at the intron 10/exon 11 boundary of the *GRN* gene was expected to affect the 5' splice site of exon 11 and result in exon skipping (Supplementary Figure 1B). The results of the bioin-

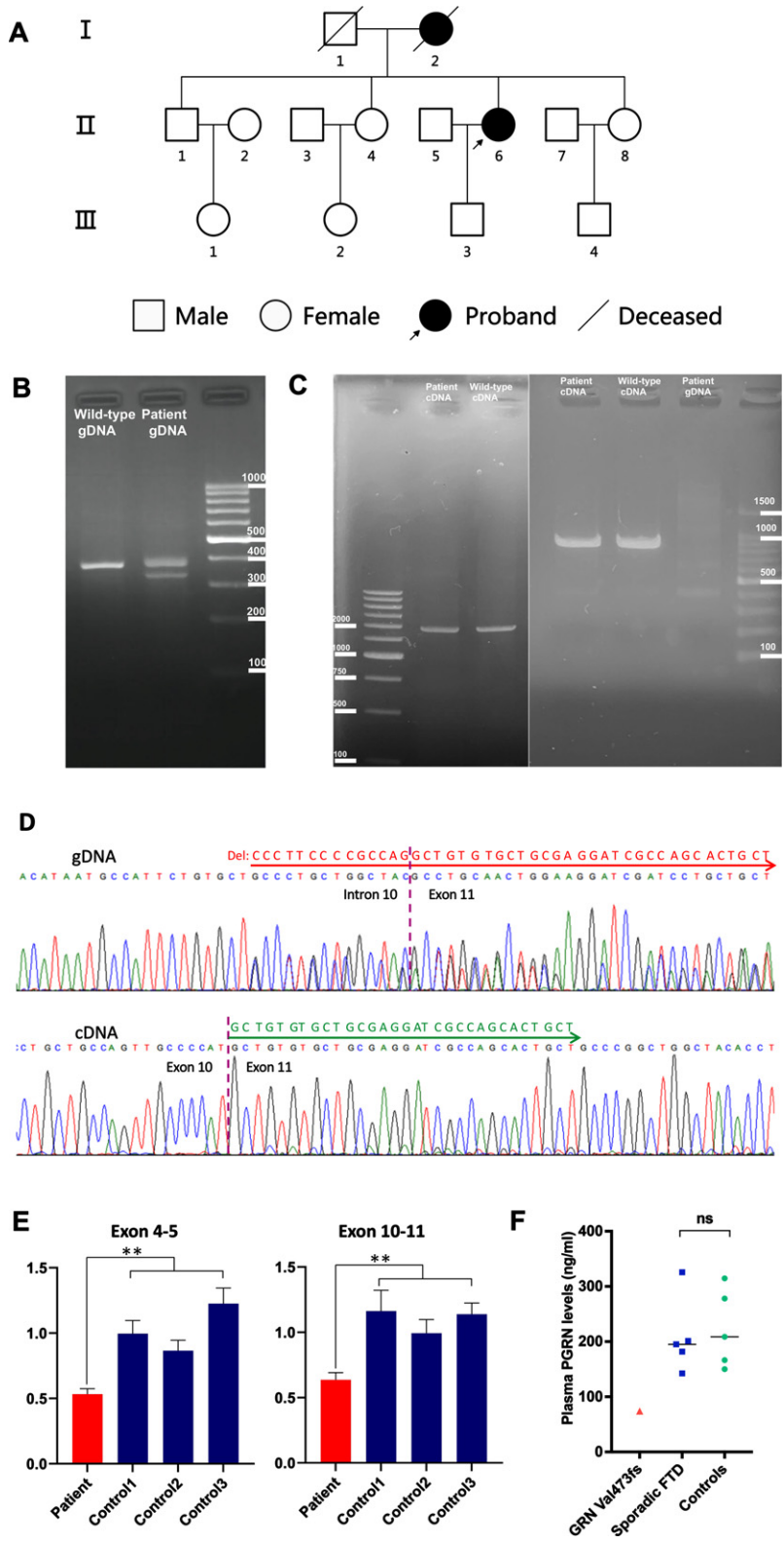


Fig. 2. (Continued)

formatic analysis showed that the deletion may also lead to a frameshift and introduction of a premature stop codon (p.Val473Argfs*8) (Supplementary Figure 1C). In both ways, the degradation of the mutated mRNA by nonsense-mediated mRNA decay (NMD) is implicated.

To confirm that the *GRN* mRNA expression level was affected by the deletion, we performed RT-PCR using total RNA from the peripheral leukocytes of the patient. Sanger sequencing of the RT-PCR products from both directions showed only canonical transcripts (Fig. 2D lower lane). Agarose gel electrophoresis of long-range RT-PCR products (exon 0 UTR–exon 12 UTR) revealed only the expected 2081-bp band in both the patient and control, with no abnormal bands (Fig. 2C). The same results were obtained using a different set of primers targeting a shorter fragment (exon 4–exon 11). Agarose gel electrophoresis of these RT-PCR products revealed only the expected 1071-bp band in both the patient and control and Sanger sequencing in both directions confirmed only canonical transcripts in the patient (Fig. 2C). Thus, we found no additional *GRN* isoforms, and the truncated transcript which is virtually absent was reduced substantially. To corroborate these results, we quantified mRNA levels in the patient's leukocytes by qRT-PCR; the results showed that the *GRN* transcript level was approximately 0.5-fold lower in the patient compared with the 3 wild-type controls (Fig. 2E).

Plasma levels of PGRN

Plasma PGRN levels in the patient carrying the Val473fs mutation, 5 FTD patients without *GRN* mutations, and 5 healthy control subjects were mea-

sured by ELISA (Fig. 2F). PGRN level in the patient with the Val473fs mutation (74.15 ng/ml) was one-third of the level in the 10 non-mutation carriers (Mean \pm SD, 216.40 \pm 21.01 ng/ml, and range, 142.47–325.80 ng/ml). There was no significant difference in median plasma PGRN levels of the 5 FTD patients without *GRN* mutations (201.24 ng/ml; range, 142.47–325.80 ng/ml) and 5 control subjects (208.61 ng/ml; range, 150.10–314.63 ng/ml) ($p = 0.76$).

Literature review

Nine publications that reported *GRN* mutations in a total of 13 Chinese patients with 12 different mutations were reviewed, including 6 missense, 4 frameshifts, 1 nonsense, and 1 splice site mutation. The *GRN* mutations were in an intron (IVS7+1G>A), exon 2 (P50fs), exon 4 (415T>C), exon 5 (560delT), exon 6 (659C>T), exon 7 (750C>A), exon 8 (898C>G), exon 10 (1352C>T and P439fs), and exon 11 (1460C>T and 1498G>A). The phenotype of *GRN* mutation carriers in China varied and included 4 bvFTD, 2 cortical basal syndromes (CBS), 1 PPA, 1 atypical PD, and 1 ALS case. The frequency of *GRN* mutation in an FTD cohort at a single center ranged from 1.2% (1/82) to 2.6% (1/38). The age of onset was <65 years and among patients whose sex was reported, there was a predominance of women (6/9, 75%). Figure 3 illustrates the *GRN* mutations identified in China, and related clinical and genetic information is shown in Table 1. Other *GRN* frameshift mutations that have been reported outside of China are listed in Supplementary Table 3.

Fig. 2. Genetic analysis of the *GRN* gene. A) Pedigree of the patient with *GRN* mutation. B) PCR amplification products across the deletion at the intron 10/exon 11 boundary of *GRN* from the patient and a wild-type control were examined by agarose gel electrophoresis. The 367-bp band corresponds to the wild-type allele. A 322-bp fragment corresponding to the heterozygous mutated allele with the 45-bp deletion was amplified from the gDNA of the patient. C) Left panel: Agarose gel electrophoresis of the long-range RT-PCR products revealing only the 2081-bp cDNA fragment corresponding to the predicted canonical transcripts in both the patient and control subject. Right panel: Agarose gel electrophoresis of shorter RT-PCR products showing only the 1071-bp band expected in both the patient and control. cDNA, complementary DNA; gDNA, genomic DNA. D) Upper lane: Sequence analysis of the gDNA PCR product of the patient revealed a c.1414-14.1444delCCCTTCCCCGCCAGGCTGTGTGCTGCGAGGATCGCCAGCACTGCT mutation in heterozygous state. Lower lane: Sanger sequencing of the RT-PCR products of the patient revealed the canonical transcripts. We found a substantial reduction in the amount of mutant allele which is virtually absent. E) *GRN* gene expression was analyzed by qRT-PCR using total RNA extracted from peripheral leukocytes of the patient with primer sets corresponding to sequences within exons 4–5 (left panel) and exons 10–11 (right panel). A \sim 50% decrease in the *GRN* product (normalized to *RPS17* level) was observed in the patient compared with the same product in the 3 wild-type control subjects. Data are expressed as Mean \pm SD of 3 independent experiments. ** $p < 0.01$ (Mann–Whitney U test). F) Plasma PGRN levels (ng/ml) in the patient carrying the *GRN* Val473fs mutation (red triangle), 5 FTD patients without *GRN* mutations (blue squares), and 5 healthy control subjects (green circles). Each data point represents an individual. Black horizontal lines indicate the median plasma PGRN levels of FTD patients without *GRN* mutations and healthy controls.

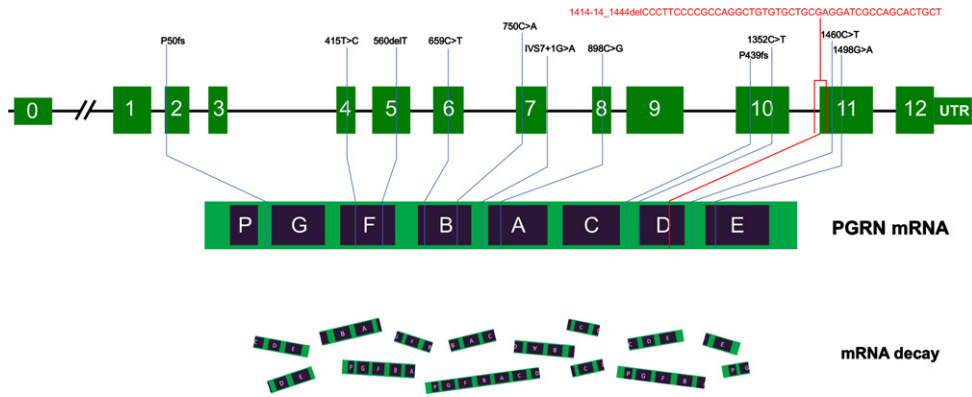


Fig. 3. Schematic representation of *GRN* mutations in China. The schematic representation of the 12 coding exons (green boxes) and UTR of *GRN* shows all pathogenic mutations identified in Chinese patients reported to date. Most of the mutations cause premature termination of the coding sequence, leading to the degradation of the mutant *GRN* mRNA by nonsense-mediated decay. The c.1414-14_1444del mutation identified in this study is indicated in red.

Table 1
Summary of the *GRN* mutations reported in Chinese patients with FTD and related disease

Author year [ref]	Exon	Amino acid change	Protein change	Phenotype	Frequency	Onset age	Sex	Family history
Masellis 2006 [30]	Splicing	IVS7+1G>A	Truncation ^a	CBS	Case	62	F	Yes
		IVS7+1G>A	Truncation ^a	CBS	Case	57	F	Yes
Shi 2016 [15]	5	560delT	L187fs ^a	PPA	1/38	64	F	No
Tang 2016 [17]	8	898C>G	Q300X ^a	bvFTD	1/52	63	M	No
Che 2017 [18]	7	750C>A	D250E ^a	FTD	1/82	62	F	NA
Chang 2018 [31]	11	1460C>T	T487I ^a	Atypical PD ^c	1/98	45	F	No
Zhang 2020 [32]	4	415T>C	C139R ^{b,d}	ALS	Case	43	F	No
Deng 2021 [33]	11	1498G>A	V500I ^a	bvFTD	Case	55	M	No
Liu 2021 [19]	10	c.1352C>T	P451L ^a	bvFTD	1/49	52	M	No
Gao 2022 [16]	10	NA	P439fs ^a	FTD	3/204	NA	NA	NA
	2	NA	P50fs ^a	FTD	/	NA	NA	NA
	6	659C>T	T220I ^a	FTD	/	NA	NA	NA
This study	11	c.1414-14_1444delCCCTTCCC-CGCCAGGCTGTGTGCTGC-GAGGATGCCAGCACTGCT	V473fs ^a	bvFTD	Case	57	F	Yes

ALS, amyotrophic lateral sclerosis; CBS, cortical-basal syndrome; bvFTD, behavioral variant frontotemporal dementia; F, female; FTD, frontotemporal dementia; M, male; NA, not available; PD, Parkinson’s disease; PPA, primary progressive aphasia. ^aNot reported in Western countries. ^bAlso reported in Western countries. *GRN* p.C139R was reported in Italy [36] and Spain [37, 38]. ^cThis patient presented with psychotic behavior at the age of 45 years. ^dThis patient carried 2 pathogenic mutations including the *NEK1* nonsense mutation p.K1210* and *GRN* mutation p.C139R.

DISCUSSION

In this study, we identified a novel pathogenic V473fs mutation of the *GRN* gene in a Chinese

woman with FTD. We also summarized all patients with *GRN* mutations reported in China and found a prevalence of 1.2%–2.6%, early disease onset, and female predominance in this population. The results

of this study expand the *GRN* mutation spectrum in China. As increasing PGRN levels has been shown to be an effective treatment for FTD [11], screening for *GRN* mutations can potentially guide treatment strategies for FTD.

We determined that our patient had haploinsufficiency due to a *GRN* mutation that caused reduced *GRN* mRNA expression and plasma PGRN level. The novel *GRN* mutation was deemed pathogenic according to the ACMG and Association for Molecular Pathology standards and guidelines [13] based on the following criteria. 1) Loss of function is a known mechanism of the disease (PVS1). 2) *GRN* mRNA level was reduced in the patient compared with healthy control subjects (PS3). 3) The mutation was located in a functional domain (PM1). 4) The mutation was absent in the healthy population (PM2). 5) The gene is highly conserved across species and computational predictions support a deleterious effect (PP3). 6) The patient's phenotype indicated a disease with single-gene etiology (PP4).

GRN mutations are rare in China [7], with a prevalence of just 1.2%–2.6% [15–19], and have been infrequently reported in other Asian countries including Japan, Philippines, India, and Korea (where they have never been observed) [20–24]. In contrast, *GRN* mutations are common in Western countries, accounting for 34.6% of mutations in patients with FTD [5]. Other gene mutations differing in prevalence in Western countries and China are *C9*, which is more common in the former, and *MAPT*, is more common in the latter [5, 7]. Such differences are mainly due to ethnicity and environmental factors. The most common *GRN* mutations in Western countries are Thr272fs, Arg493X, IVS7–1G→A, Cys31fs, Gly35fs, and Ala9Asp [5], but these are not present in the Chinese population. In our review, we identified mutations in exons 2, 5, 6, 7, and 8, 2 in exon 10, and 3 in exon 11; there were no specific clustering tendencies compared with mutations reported in Western countries [25].

We observed atrophy and hypometabolism in the left frontal, temporal, and parietal lobes in our patient, which is consistent with the asymmetric atrophy reported in *GRN* mutation carriers [25–27]. The white matter hyperintense signal was found in our patient, which has also been previously reported in other patients with *GRN* mutations [20, 28]. Amyloid and Tau PET were negative because patients with *GRN* mutation had TAR DNA-binding protein 43 (TDP43) protein inclusions [29].

The clinical phenotypes for *GRN* mutations vary; most patients in our review presented with bvFTD and others with CBS, PSP, atypical PD, or ALS [30–33]. Left-side temporal lobe atrophy may contribute to language deficits whereas right-side frontal lobe atrophy has been linked to psychoses and behavioral deficits in previous cases [25, 34]. Our patient mainly presented with semantic variant PPA, which was associated with functional involvement of left-side brain regions as determined by ¹⁸F-FDG-PET/MRI. Additionally, we observed female predominance among Chinese patients with *GRN* mutations, consistent with the findings of a meta-analysis showing a higher prevalence of *GRN*-related FTD among women [35].

Our study had some limitations. First, the sample size of the review was small because *GRN*-related FTD is rare in China. Second, there may have been publication bias in the review because genetic screening is not common in some rural areas of China. Larger, multicenter genetic studies are needed to confirm the frequency of *GRN* mutations in China.

Conclusion

In conclusion, we identified a novel pathogenic *GRN* gene mutation (V473fs) in a patient with FTD. The prevalence of the mutation was 1.2%–2.6% among Chinese patients with FTD, who were mostly female and had an early disease onset. Our findings expand the mutation spectrum of *GRN* in FTD and provide a basis for the development of targeted therapies.

ACKNOWLEDGMENTS

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CONFLICT OF INTEREST

Liyong Wu is an Editorial Board Member of this journal but was not involved in the peer review process, nor had access to any information regarding its peer review.

DATA AVAILABILITY

The datasets used and analyzed in the current study are available from the corresponding author upon reasonable request.

SUPPLEMENTARY MATERIAL

The supplementary material is available in the electronic version of this article: <https://dx.doi.org/10.3233/JAD-230052>.

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