PRDOA 9 (2023) 100213

Contents lists available at ScienceDirect

Clinical Parkinsonism & Related Disorders

journal homepage: www.sciencedirect.com/journal/clinical-parkinsonism-and-related-disorders

Case Reports

# A case of familial frontotemporal dementia caused by a progranulin gene mutation

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ARTICLE INFO

*Keywords:*
Frontotemporal dementia
FTD
Progranulin, GRN
Phenotypic heterogeneity

ABSTRACT

After Alzheimer's disease, Frontotemporal dementia (FTD) is the most common cause of early-onset dementia. Several genetic mutations have been identified in familial FTD, with mutations in progranulin (GRN) accounting for approximately 20–25% of familial FTD cases and about 10% of total FTD cases. We report the case of a familial FTD patient with atypical parkinsonism who was found to have *GRN* frontotemporal dementia (*GRN*-FTD) with a pathogenic splice site mutation (c.709-2A > G) and notable phenotypic heterogeneity among family members.

## 1. Introduction

Frontotemporal dementia (FTD) encompasses a spectrum of progressive neurodegenerative disorders, with three primary clinical syndromes. These include: behavioral variant FTD (bvFTD), nonfluent-agrammatic variant primary progressive aphasia (nfvPPA), and semantic variant primary progressive aphasia (svPPA) [1]. The clinical presentation is highly variable and may include changes in personality, behavior, and speech, as well as parkinsonism and motor neuron disease [1,2]. After Alzheimer's disease, FTD is the most common cause of early-onset dementia [1]. A family history of FTD is the only known risk factor, with 20–50% of FTD patients reporting a positive family history [3]. Several genetic mutations have been identified in familial FTD, with mutations in the open reading frame of chromosome 9 (*C9orf72*), microtubule-associated protein tau (*MAPT*), and progranulin (*GRN*) being the most common [3]. Here, we report the case of a familial FTD patient with atypical parkinsonism who was found to have *GRN* frontotemporal dementia (*GRN*-FTD) due to a pathogenic splice site mutation (c.709-2A > G) and notable phenotypic heterogeneity among family member.

## 2. Case report

The patient was a 73-year-old, right-handed woman with a history of non-Hodgkin lymphoma, cervical spinal stenosis, and depression who presented to the movement disorders clinic for evaluation of atypical parkinsonism and cognitive concerns. At the time of evaluation, she described a three-year history of difficulty with movements and manipulation of her left arm and a progressive history of imbalance with multiple falls, requiring the use of a walker to ambulate. She required assistance with several basic activities of daily living, including getting dressed and transferring out of bed, and reported difficulty following recipes when cooking. Her family reported decreased engagement in conversations and increased monosyllabic responses to questions. She also reported being more withdrawn and apathetic over the past two years and had a 20-pound weight gain over one year, which she attributed to eating more sweets.

Prior to her evaluation at our clinic, her workup included an electromyography/nerve conduction study of the left arm and both legs, which was normal. She had a fluorodeoxyglucose positron emission tomography-computed tomography (FDG-PET/CT) scan, which showed hypometabolism in the supratentorial white and grey matter, most

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https://doi.org/10.1016/j.prdoa.2023.100213
Received 31 May 2023; Received in revised form 22 July 2023; Accepted 4 August 2023
Available online 6 August 2023

severe in the right frontal lobe (Fig. 1). Her magnetic resonance imaging (MRI) study of the brain without contrast was notable for diffuse atrophy, particularly in the right greater than left frontal and parietal regions, as well as atrophy of the midbrain, affecting the right midbrain more than the left (Fig. 1). She had been diagnosed with Parkinson's disease at an outside facility and started on Carbidopa-Levodopa (10–100 mg), with a total daily Levodopa dose of 300 mg. Previous trials to increase the dose had caused vertigo. The patient did not notice any motor benefit on Levodopa.

Her family history was significant for autopsy-confirmed frontotemporal dementia diagnosed in her mother and older sister, and a history of unspecified dementia in her maternal grandfather and maternal uncle (Fig. 2). Our patient's sister with FTD had a clinical course most notable for symptoms of progressive aphasia and executive dysfunction that began around age 55. The neuropathology results from our patient's sister showed frontotemporal lobar degeneration with ubiquitin immunoreactive deposits (FTLD-U) within neurons and neurites in the neocortex, basal ganglia and hippocampus, as well as neuritic plaques, tau-immunoreactive neurons, and neurofibrillary tangles. Staining for TDP-43 was not performed. Our patient's mother's presentation was notable for parkinsonism, muteness, and personality changes which started around age 72. Neuropathology results from our patient's mother showed severe cortical atrophy, most pronounced in bilateral frontal lobes, and severe neuronal loss present in the substantia nigra, with scattered synuclein and ubiquitin-positive Lewy bodies.

Her initial physical examination in our clinic was notable for asymmetric left predominant limb rigidity, bradykinesia, dystonia, and myoclonus, as well as mild ideomotor apraxia in both hands. Extraocular movements were full but she was noted to have saccadic smooth pursuits and square wave jerks in primary gaze. An applause sign was present. She had hyperreflexia throughout, more notably in the left leg compared to the right. On gait assessment, she had a slightly stooped posture, shortened stride length on the left, and *en bloc* turns. She displayed postural instability, demonstrated by the absence of a postural response when pulled backward. She scored 24/30 on the Montreal Cognitive Assessment test (v.8.1), with deficits in visuospatial and executive function, and 11/18 on the Frontal Assessment Battery [4,5].

Our patient met Armstrong et al. clinical criteria for probable Corticobasal Syndrome (CBS); however, because of her known family history with a distinct possibility of a genetic contribution, we recommended genetic testing [6]. Several months after her initial clinic appointment, she was placed in a memory care facility due to the progression of her cognitive deficits and gait difficulties. Genetic testing via the neurodegenerative gene panel including dementia, parkinsonism, and ALS genes from Centogene Labs identified a disease-causing splice site mutation (c. 709-2A > G) in the *GRN* gene, confirming the diagnosis of *GRN*-FTD.

## 3. Discussion

*GRN* mutations are responsible for approximately 20–25% of familial FTD cases and about 10% of total FTD cases [7]. *GRN*-FTD is inherited in an autosomal dominant pattern, as displayed in our patient's significant family history. *GRN* mutations were first discovered as a major genetic cause of FTD in 2006. Subsequently, TDP-43 was identified as the main associated protein deposition in histopathological studies [2]. Frequent Lewy body copathology was previously described, which was also observed in our proband's mother. Since then, over 70 *GRN* mutations have been reported [1–3].

The *GRN* gene, located on chromosome 17q21.32, encodes for the protein progranulin [1]. Progranulin is responsible for activating signal cascades in several processes including inflammation and development [1]. GRN has been shown to be expressed in both Purkinje and pyramidal cells of the cerebral cortical neurons, as well as the hippocampus [8]. Progranulin mutations have been shown to be associated with hippocampal sclerosis, likely secondary to the large levels of progranulin genes found in the hippocampus [9]. While the exact role of Progranulin in the central nervous system is unknown, *GRN* mutations result in a premature stop codon ultimately leading to haploinsufficiency [3,8]. The c.709-2A > G splice-acceptor site mutation in *GRN* is predicted to skip exon 8 of the transcript, resulting in a frameshift with a premature stop codon (p.A237TfsX6) and non-sense mediated mRNA decay [10]. Prior work has demonstrated decreased levels of progranulin in the plasma of mutation carriers, consistent with haploinsufficiency as the molecular defect underlying this severe neurodegenerative syndrome [10]. One hypothesis for the role of progranulin gene mutations in the pathogenesis of FTD is that *GRN* mutations result in TDP-43 accumulation, ultimately leading to neurodegeneration [8,9].

Individuals with *GRN*-FTD may present with behavioral variant FTD or the primary progressive aphasia variant (further divided into either progressive non-fluent aphasia or semantic dementia), as well as concurrent parkinsonism [1,3,7]. In rare instances, patients with pathogenic *GRN* mutations present clinically with Lewy body dementia [11]. Extrapyramidal signs typically develop after changes in behavior and speech and occur in approximately 40% of people with *GRN*-FTD [1,3]. These extrapyramidal signs typically include dystonia and asymmetric parkinsonism along with cortical involvement, together consistent with CBS [3]. Our patient's clinical presentation with left arm dystonia, predominantly left-sided bradykinesia, and other parkinsonian signs, fit the typical *GRN*-FTD phenotype. Interestingly, a Progressive Supranuclear Palsy (PSP)-like variant has also been described with *GRN*-FTD, and our patient had eye movement abnormalities and midbrain atrophy, as frequently seen in PSP [12]. CBS and PSP represent a clinical spectrum and have overlapping features, including parkinsonism, frontal lobe dysfunction and apraxia.

Neuroimaging in patients with *GRN* mutations typically shows

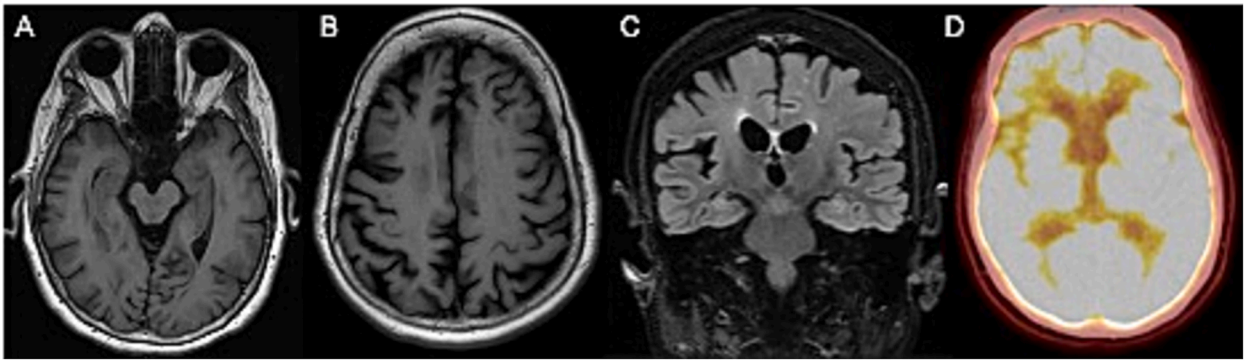


**Fig. 1.** MRI and FDG-PET CT. Axial non-contrast MRI brain shows diffuse atrophy, particularly in the right greater than left frontal and parietal regions (B and C) and right greater than left midbrain atrophy (A). Fluorodeoxyglucose positron emission tomography-computed tomography scan shows hypometabolism in the supratentorial white and grey matter, most severe in the right frontal lobe (D).

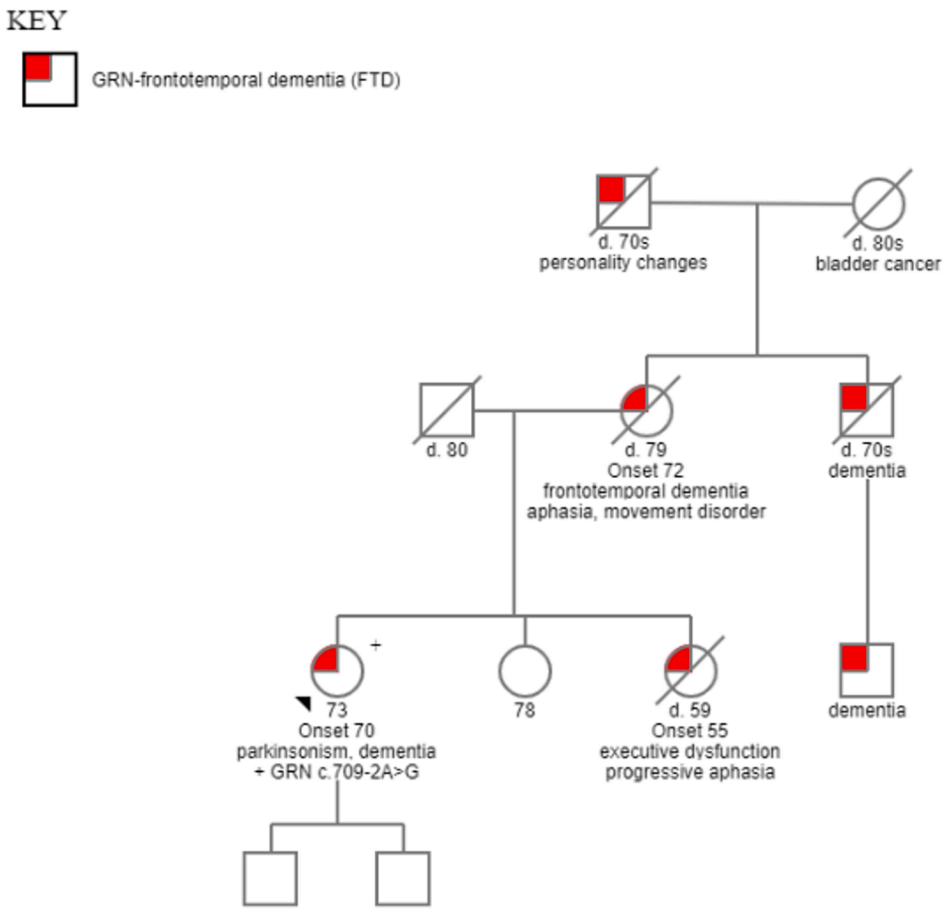


**Fig. 2.** Family pedigree. This family pedigree includes four generations. Our proband is indicated by an arrowhead. An autosomal dominantly inherited neurodegenerative process is suggested based on the family history provided.

asymmetric cerebral atrophy, as seen in our patient (Fig. 1) [1,3]. Compared with other monogenic forms of FTD, *GRN* mutation carriers tend to have a faster rate of atrophy [1]; this is observed in the frontal, parietal, temporal, and occipital lobes, with more atrophy in the parietal-occipital regions when compared to *MAPT* mutation carriers. This pattern may explain the CBS phenotype that can be seen in *GRN*-FTD.

Detailed phenotypic and family history data are important to highlight the variability of the clinical presentation of a single mutation segregating across multiple generations with *GRN*-FTD [8,13,14 ]. This phenotypic spectrum was clearly observed in our patient's family: while the proband presented with a CBS phenotype, her mother had more of a typical parkinsonian presentation, with scattered synuclein and ubiquitin-positive Lewy bodies on pathology to match, while her sister had more of a primary progressive aphasia presentation with FTLD-U as well as neuritic plaques, tau-immunoreactive neurons and neurofibrillary tangles. Spina et al. also demonstrated single-family heterogeneity within family members diagnosed with FTD caused by an IVS6-2A > G *GRN* mutation [13]. In this case series, the proband's mother had more of a Parkinsonian presentation, like our patient's mother, while the proband's presentation was notable for a primary progressive aphasia with reduced vocabulary, which later progressed to muteness and mild ideomotor apraxia [13]. *GRN*-FTD is an important diagnosis to keep in mind for patients presenting with parkinsonism, speech changes, and cortical signs, particularly in those with a family history of FTD or unspecified dementia.

## Funding

S.W.S. was supported by the Intramural Research Program of the National Institute of Neurological Disorders and Stroke, part of the U.S. National Institutes of Health (program #: 1ZIANS003154).

## Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: S. W.S. serves on the scientific advisory board for the Lewy Body Dementia Association and the Multiple System Atrophy Coalition. S.W.S. received research support from Cerevel Therapeutics.

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