Corticobasal Syndrome Associated With the A9D Progranulin Mutation

Salvatore Spina, MD, Jill R. Murrell, PhD, Edward D. Huey, MD, Eric M. Wassermann, MD, Pietro Pietrini, MD, PhD, Jordan Grafman, PhD, and Bernardino Ghetti, MD

Abstract
Corticobasal syndrome is characterized by cortical dysfunction and l-dopa-unresponsive Parkinsonism, with asymmetrical onset of clinical presentation and evidence of atrophy and/or hypometabolism at neuroimaging. Recently, the heterogeneous pathologic substrate of corticobasal syndrome has been further expanded to include cases with pathologic diagnosis of frontotemporal lobar degeneration with ubiquitin/TDP-43 (TAR DNA binding protein 43)-positive inclusions associated with Progranulin (PGRN) mutations. We report a family in which several individuals have been affected with a dementia/movement disorder phenotype. The proband presented at age 45 with spontaneous left arm levitation, ideational apraxia, asymmetric parkinsonism, and dystonia. Subsequently, he developed limb-kinetic apraxia, left-side hemineglect, memory loss, and executive dysfunction. Magnetic resonance imaging and [18F]fluorodeoxyglucose-poitron emission tomography studies revealed severe cerebral cortical atrophy and hypometabolism, which were significantly more pronounced in the parietal lobes (right > left). Neuropathologic examination displayed the highest degree of degeneration and ubiquitin/TDP-43 pathology in the proband’s parietal areas. Genetic analysis revealed the presence of the c.26C>A PGRN mutation in 1 allele. This mutation has been reported in association with hereditary-amyloid polyneuropathy and myotonic dystrophy. The peculiar findings observed in this patient indicate that the parietal lobe may represent the most vulnerable anatomical area in some of the PGRN-associated frontotemporal lobar degeneration with ubiquitin/TDP-43-positive inclusion cases.

Key Words: Alien limb, Apraxia, Frontotemporal lobar degeneration, Hemineglect, Parietal lobe, Progranulin, TDP-43.

INTRODUCTION
The term “corticobasal syndrome” (CBS) has been proposed to designate a clinical phenotype characterized by symptoms and signs of cortical dysfunction (such as ideomotor or constructional apraxia, speech apraxia, progressive nonfluent aphasia, cortical sensory loss, alien hand syndrome [AHS], visual or sensory hemineglect, and myoclonus), as well as signs of extrapyramidal impairment (such as limb rigidity or dystonia) lacking significant response to l-dopa (1). CBS has an insidious onset followed by a progressive course. Signs and symptoms are initially focal or asymmetrical and correlate with neuroimaging evidence of asymmetric atrophy and/or hypometabolism, which are maximal in the parietofrontal cortical areas (1). The pathologic substrate of CBS is heterogeneous and includes that of corticobasal degeneration (CBD), Alzheimer disease, Pick disease, progressive supranuclear palsy, dementia lacking distinctive histopathology, Creutzfeldt-Jakob disease, diffuse Lewy body disease, and frontotemporal lobar degeneration with ubiquitin (Ub) and TDP-43 (TAR DNA binding protein 43)-immunoreactive (ir) inclusions (FTLD-U) (1–9).

The majority of cases of CBS are sporadic. However, a clinical phenotype closely resembling that of CBS has been described in individuals belonging to families in which several additional subjects were affected with either dementia and/or movement disorder (6). In some of these families, the genetic base of the familial disorder has been found to be associated with the inheritance of a pathogenic mutation in either the Microtubule Associated Protein Tau (MAPT) gene or in the Progranulin (PGRN) gene, both located in chromosome 17q21 (10–14). MAPT mutations are associated with the clinicopathologic phenotype of frontotemporal dementia and Parkinsonism linked to chromosome 17, a group of autosomal dominant frontotemporal dementia (FTD) syndromes that are pathologically characterized by the deposition of hyperphosphorylated tau protein in the CNS (15). In contrast, PGRN mutations are associated with the pathologic phenotype of FTLD-U (16, 17). Extensive literature on MAPT mutations has shown the existence of considerable inter-
intrafamilial phenotypic heterogeneity (18). Similarly, the recent reports on PGRN mutations suggest the presence of relevant clinical and pathologic variability among different families as well as among affected individuals from the same kindred (10, 12, 13, 19–23).

We report a family in which several individuals have been affected with a dementia/movement disorder phenotype. In the proband the clinical presentation was consistent with CBS. Neuroimaging studies revealed severe atrophy and reduced glucose metabolism in the cerebral cortex, with predominant involvement of the right cerebral hemisphere compared with that of the left one, as well as involvement of the parietal lobes compared with that of frontal and temporal lobes. Neuropathologic examination revealed abundant ubiquitin and TDP-43-ir neuronal inclusions, particularly evident in the parietal cortex, consistent with a diagnosis of FTLD-U. Genetic analysis revealed the c.26C>A PGRN mutation in 1 allele. The analysis of this case highlights the possibility that parietal lobes may be a main target of neurodegeneration in PGRN-associated FTLD-U cases, thus, extending the knowledge of the phenotypic variability of PGRN mutations and pathologic heterogeneity of CBS.

MATERIALS AND METHODS

Subject

The proband was diagnosed with CBD and was referred to the National Institute of Neurological Disorders and Stroke (NINDS) Cognitive Neuroscience Section by an outside neurologist. The diagnosis of CBS was ascertained by one of us (E.M.W.), according to the proposed criteria, and the subject was enrolled under the NINDS Corticobasal Syndrome research protocol (1). As part of this study, the patient underwent a neurologic and neuropsychologic evaluation as well as neuroimaging, which included magnetic resonance imaging (MRI) and [18F]fluorodeoxyglucose-pet emission tomography (18F-FDG-PET). A written informed consent for the research protocol and postmortem evaluation as well as neuroimaging, which included magnetic resonance imaging (MRI) and [18F]fluorodeoxyglucose-pet emission tomography (18F-FDG-PET). A written informed consent for the research protocol and postmortem examination of the brain was obtained from the patient’s durable power of attorney before enrollment. The institutional reviews boards of the NINDS and Indiana University approved the clinical studies and neuropathologic studies, respectively.

Neuropsychologic Testing

As part of the neuropsychologic evaluation, the following cognitive domains were assessed: general cognition (Wechsler Adult Intelligence Scale–3rd edition [WAIS-III] and Mattis Dementia Rating Scale 2 [MDRS2]); language (single word reading of the National Adult Reading Test); memory (Wechsler Memory Scale–3rd edition); visuospatial perception (Visual Object and Space Perception [VOSP] Battery); motor control (Finger Tapping Test, Grooved Pegboard [Lafayette Instruments, Lafayette, IN] and Test of Limb Apraxia); and executive function (Delis-Kaplan Executive Function System). Mood and behavioral symptoms were also assessed (Beck Depression Inventory, 2nd edition [BDI], Neuropsychiatric Inventory [NPI], and Neurobehavioral Rating Scale [NRS]) (24–35).

Neuroimaging

MRI was carried out using a Signa General Electric 1.5 Tesla scanner. High-resolution anatomical images were acquired in the sagittal (T1-weighted) and axial (T1-weighted, T2-weighted, and fluid attenuation inversion recovery). In addition, 3-dimensional spoiled-gradient recalled sequences were acquired in the sagittal, axial, and coronal planes. An [18F]FDG-PET scan was performed on a GE Advance 3D scanner (4.25 mm slice separation, 35 slices, axial field of view 15.3 cm, transverse field of view 55.0 cm) as previously described (36).

Neuropathology

The brain was cut along the mid-sagittal plane. The left hemibrain was fixed in 10% buffered formalin, whereas the right hemibrain was frozen for genetic and biochemical studies. Sections were obtained from the following regions: superior and middle frontal gyri, cingulate gyrus, superior and middle temporal gyri, amygdala, superior parietal lobule, occipital cortex, basal ganglia at the level of the anterior commissure, thalamus at the level of the subthalamic nucleus, anterior and posterior hippocampus, cerebellar cortex, dentate nucleus, midbrain, pons, and medulla. Tissue was processed for classic histology and immunohistochemistry according to protocols published previously (37). Immunohistochemistry was performed using antibodies specific for: ubiquitin (1:100; DakoCytomation, Carpinteria, CA), TDP43 (rabbit polyclonal antibody, 1:100; ProteinTech Group, Chicago, IL), phosphorylated tau (AT8; Innogenetics, Antwerp, Belgium), β-amyloid (10D5, 1:100; Elan Pharmaceuticals, South San Francisco, CA), glial fibrillary acidic protein (1:100; DakoCytomation), prion protein (3F4, 1:800; gift from Dr. Kascak, Institute for Basic Research in Developmental Disabilities, Staten Island, NY), αβ crystallin (1:1000; Chemicon, Billerica, MA), phosphorylated neurofilament (SMI31, 1:1000; Covance Research Products Inc., Berkeley, CA) and α-synuclein (38).

Genetic Analyses

Genomic DNA was extracted from a frozen sample of cerebellum using a standard protocol (39). The entire PGRN coding region and flanking intronic sequences were analyzed. Polymerase chain reaction was done using 50 ng of genomic DNA and the primers described previously (36). The amplified products were gel-purified using the Qiaquick Gel Extraction Kit (Qiagen, Valencia, CA) and subjected to asymmetric amplification using the DTCS Quick Start Kit (Beckman Coulter, Fullerton, CA). Products were analyzed on a CEQ 8000XL DNA analysis system (Beckman Coulter). The resulting DNA sequences were compared to the known PGRN sequences (http://www.ncbi.nlm.nih.gov).

RESULTS

Clinical History

This right-handed man was evaluated at age 48. During the previous 3 years he experienced progressively reduced
control of his left arm’s movements. Initially, symptoms were characterized by an involuntary elevation of the left arm while the patient performed intentional movements with the contralateral limb. Subsequently, he developed increasing clumsiness and dystonic postures of the left arm. He reported increasing difficulties in carrying out his job as a photographer because of reduced ability to plan the sequence of actions required. He had severe difficulties dressing, including donning a shirt backwards or forgetting to put his left arm in. He stopped driving because of inability to plan the route, developed deficits in managing finances and on some occasions, he was disoriented for time. He reported falling on several occasions due to postural imbalance.

On the physical examination he appeared alert, appropriate, and cooperative. His speech was fluent and free of paraphasic errors; however, impaired abstract word retrieval and elements of superordinate substitution were occasionally noted. Slowed saccades, saccadic breakdown of pursuit movements, and nystagmus at the extreme lateral gaze were noted. Strength and tone were normal except for increased tone of the left arm. There was a bilateral tendency to hold postures after manipulating objects or pantomiming (left > right). Finger movement dexterity was severely reduced on the left hand. Rapid alternating movements were bilaterally impaired (left > right). The finger-to-nose test was past-pointing and slow bilaterally. Deep tendon reflexes were normal on the right and slightly hyperactive on the left. A jaw jerk was also noted. Proprioception and graphesthesia were reduced on the left side. He was able to walk with the help of a cane. His gait was remarkable for widening of the base, abnormal posturing of the trunk, lack of arm swinging on the left and delayed step initiation in response to the movement of the trunk (magnetic gait). Information on the progression of the clinical phenotype is not available. The proband died at age 51 after 6 years of disease duration.

**Family History**

The proband’s father presented with behavioral changes and dysexecutive symptoms, followed by cognitive decline, incoordination, a tendency to fall, and leg rigidity (left > right). He developed difficulties in controlling his left arm’s movement but never experienced AHS. He had word-finding difficulties that developed into mutism in his last year of life. He was clinically diagnosed with Alzheimer disease and died at the age of 73; no autopsy was performed. Among the proband’s father’s siblings, 2 have been diagnosed with dementia and 1 with Parkinson disease; 1 of them died, but a neuropathologic assessment was not done.

**Neuropsychologic Assessment**

Among the different subtests of the WAIS-III, the proband achieved an aged-scale score of 8 on Vocabulary and 5 on Picture Arrangement. These scores are in the below average to impaired range. The patient’s MDRS2 total score of 116 was in the moderately impaired range. His performance on the reading test was normal. Visuospatial perception was within normal limits. His left hand performances on tests of motor control were severely impaired. Significantly, his finger-tapping performances were of an average of 61.6 taps with his dominant hand and 29.3 taps with his left hand. He required 171 seconds to carry out the Grooved Pegboard test with the right hand but was unable to execute the test using the left hand. His performance on the test for limb apraxia was mildly impaired, and he performed better in response to verbal commands than to imitation. On some occasions, an alien-limb phenomenon involving his left arm was noted. He presented mild difficulty on the cube-counting

![FIGURE 1. Clock copying drawn by the proband displaying left-sided hemispatial neglect (top). Proband’s drawings (copy [middle] and recollection [bottom]) of the USA map, further emphasizing the presence of left-sided hemineglect. Note that when asked to indicate locations in the USA map drawn by memory the proband gave an accurate relative spatial localization of markers such FLA (Florida), CHAR (Charlotte, South Carolina), W (Washington, DC), CIN (Cincinnati, Ohio), and SF (San Francisco, California).](http://jnen.oxfordjournals.org/)

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subtest of the VOSP battery. His drawings showed left-sided neglect (Fig. 1).

His verbal, nonverbal, and working memory functions were all moderately impaired. When tested for executive functioning, the proband showed difficulties in conceptual shifting, response-inhibition, planning, and categorization. His verbal reasoning and letter fluency were intact. He obtained a score of 26 on the BDI, which is indicative of moderate emotional distress. The total scores of 35 at the NPI (apathy/indifference 8; agitation, depression, disinhibition, irritability/emotional lability 6; anxiety 3) and 41 at the NRS (disorientation 5; memory deficits 4; disinhibition, depressive mood, and comprehension deficit 3) are indicative of mild behavioral dysfunctions.

**Brain Imaging**

The MRI of the brain revealed moderate to severe atrophy of the cerebrum with significantly more extensive involvement of the right hemisphere compared with the left one. Particularly striking was the severity of the narrowing of the gyri and dilation of the sulci at the level of the right parietal lobe and, to a lesser extent, of the right frontal lobe (Fig. 2). In the left cerebral hemisphere, the degree of atrophy was more severe in the parietal lobe than in the frontal lobe. A single punctuate focus of T2 time prolongation was observed in the left parietal lobe. The [18F]FDG-PET scan showed a moderate to severe reduction of glucose metabolism in the right frontal, temporal, and parietal cortices with relative sparing of the left hemisphere and subcortical nuclei (Fig. 3).

**Neuropathology**

The fresh brain weight was 980 g (left hemibrain, 520 g; right hemibrain, 460 g). In the dorsolateral portion of the left cerebral hemisphere, severe atrophy was evident in the superior and middle frontal gyri, superior parietal lobule, supramarginal gyrus, and angular gyrus. In the mesial surface of the brain, atrophy was particularly evident in the superior frontal gyrus and precuneus. In contrast, there was only mild atrophy of the temporal and occipital lobes and minimal atrophy of the hippocampus and parahippocampal gyrus. The corpus callosum was severely reduced in thickness, particularly in its posterior portion. The bulk of the centrum semiovale was also reduced. The lateral ventricle was extensively enlarged. The thickness of the cortical ribbon was ~1 mm in the parietal lobe (Brodmann’s area [BA] 3) and ~2 mm in the frontal lobe (BA 4) (approximately 50% reduction), as well as ~3 mm in the temporal lobe.

![FIGURE 2. Coronal spoiled-gradient recalled (A) and axial T1-weighted (B) magnetic resonance (MR) images of the proband's brain, in radiologic orientation, displaying severe atrophy of the right frontoparietal regions with a significant anteroposterior-positive gradient of involvement. In the left cerebral hemisphere, moderate atrophy of the parietal lobe is also seen. Note the significant asymmetric enlargement of the lateral ventricles (right > left) and the relative sparing of the temporal lobes. Sagittal T1-weighted MR images (C) from the right (first 2 panels from the left) and left (first 2 panels from the right) cerebral hemispheres, taken at the same distance from the midsagittal plane, display the asymmetric predominant involvement of the right hemisphere in the disease process. In the mesial portion of both cerebral hemispheres, the significant involvement of superior frontal gyrus and precuneus is shown.](http://jnen.oxfordjournals.org/)

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lobe (BA 41) (average) (40). The head of the caudate nucleus was moderately flattened and the body was reduced in bulk, as was that of putamen, amygdala, and thalamus. The cerebellum was mildly atrophic. Substantia nigra and locus coeruleus were moderately depigmented.

The histologic findings in the cerebral cortex and subcortical nuclei are displayed in the Table. Immunohistochemical findings are shown in Figure 4. A mild loss of axons and myelin and moderate astrogliosis were observed in the subcortical white matter. In the brainstem, substantia nigra and locus coeruleus displayed moderate neuronal loss. Ub-ir and TDP-43-ir neuronal cytoplasmic inclusions and dystrophic neurites were abundant in the second cortical layer of the parietal and, to a lesser extent, frontal cortices. They were also found in a significantly lower number in the superior/middle temporal and parahippocampal cortices as well as in the dentate gyrus, caudate nucleus, putamen, amygdala, and thalamus (Fig. 4A–D). Ub-ir and TDP-43-ir neuronal intranuclear inclusions were overall infrequent and mostly confined to the frontal, temporal, parietal, and cingulate cortices, dentate gyrus, and striatum (Fig. 4A–C, E). In the subcortical white matter, TDP-43-ir thread-like

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<th>Neuronal Loss</th>
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<td>Caudate nucleus</td>
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<td>Putamen</td>
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<td>Globus pallidus</td>
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<td>Substantia innominata</td>
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<td>Thalamus</td>
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<td>Subthalamic nucleus</td>
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NII, TDP-43-immunoreactive (ir) neuronal intranuclear inclusions; NCI, TDP-43-ir neuronal cytoplasmic inclusions; DN, TDP-43-ir dystrophic neurites; -, absent; +, mild; ++, moderate; ++++, severe.
deposits were frequently noted (Fig. 4F). In addition, TDP-43-ir coiled body-like deposits were occasionally noted in close proximity to oligodendroglial cells (Fig. 4G). A few tau-ir neurons and neurites were seen in the frontal cortex, transentorhinal cortex, and locus coeruleus. No α-synuclein, prion protein, or Aβ-protein-ir deposits were found. No αB-crystallin-ir or hyperphosphorylated neurofilament-ir ballooned neurons were observed.

**Genetics**
A cytosine to adenine transversion at position 26 in exon 1 of PGRN (c.26C>A) was found in 1 allele. This change is predicted to cause an Ala to Asp substitution at residue 9 (Ala9Asp) in the signal peptide of progranulin.

**DISCUSSION**
We have identified a family in which a dementing and/or a movement disorder was diagnosed in several individuals from different generations. In the proband, who presented with CBS, the neuropathologic examination displayed findings consistent with FTLD-U. Genetic analysis revealed the c.26C>A PGRN mutation in 1 allele. This mutation occurs in the signal peptide of progranulin and is predicted to alter targeting and translocation of progranulin across the
membranes of the endoplasmic reticulum. This change is associated with reduced levels of the mutant mRNA for reasons that are not yet completely understood (12).

The proband presented with spontaneous left arm levitation, ideational apraxia, asymmetric parkinsonism, and dystonic postures of the hands. This presentation is consistent with the diagnosis of CBS, according to the proposed criteria (1). Later in the disease course, features of limb-kinetic apraxia, gait apraxia, dressing apraxia, temporo-spatial disorientation, memory loss, and executive dysfunction became relevant. In addition, language and behavior became mildly impaired.

Spontaneous arm levitation, in the absence of grasp reflex, groping behavior, and intermanual conflict is referred to as the posterior variant of AHS (41, 42). The posterior variant of AHS has been associated with ischemic lesions involving the parietal lobe and/or the posterior thalamus of the nondominant hemisphere (42). Ideational apraxia, a high-order disorder of goal-directed sequencing of actions, is a well-known consequence of extended pathology of the left parietal lobe, variably associated with further involvement of frontal, temporal, occipital, or subcortical brain regions (43–47).

The proband’s clinical presentation was thus indicative of a predominant and early involvement of the parietal lobes in the disease process (48). This topographic diagnosis was supported by evidence of left-side inattention and visuconstructional impairment. Features of ideomotor apraxia, such as the presence of temporal and/or spatial errors in the execution of movements as well as improper spatial orientation and use of body parts as objects, were not observed (49). Consistently, there was no significant difference between the proband’s performance of transitive actions and intransitive actions; performances on imitation were poorer than that on response to verbal commands (50, 51). The later development of limb-kinetic apraxia, apraxia of gait, dysexecutive symptoms, and language deterioration are suggestive of a delayed involvement of the frontal lobes in the disease process (52–54).

Indeed, a correlation between the clinical symptoms and pathology as demonstrated by neuroimaging was achieved in vivo through the demonstration of severe atrophy and reduced glucose metabolism of the parietal lobes (right > left) and, to a lesser extent, of the superior and middle frontal gyri (right > left). These findings were consistent with the higher degree of atrophy and the abundance of Ub-ir/TDP-43-ir deposition observed in the parietal areas at the neuropathologic examination. Parkinsonism and dystonic postures may be explained by the concomitant pathology of the striatum and substantia nigra.

To date, the c.26C>A (p.A9D) PGRN mutation has been reported in affected individuals from a large FTLD-U kindred of European ancestry (HDDD2), as well as in 3 independently ascertained individuals with FTD/FTLD-U (12, 20). The neuropathologic phenotype in the affected individuals from the HDDD2 family presented interesting similarities with that of our case. Remarkably, severe neuronal loss and abundant Ub-ir neuronal intranuclear inclusions, neuronal cytoplasmic inclusions, and dystrophic neurites were present in the parietal cortex. However, in the HDDD2 cases, the extent of pathology in the parietal lobe was consistently lower than that in the frontal and temporal areas and the clinical phenotype was that of hereditary dysphasic disinhibition dementia (HDDD) or Alzheimer-like dementia (20). Gass et al (12) and Josephs et al (19) reported 2 subjects in which the c.26C>A PGRN mutation was associated with FTLD-U, the presence of neuronal intranuclear inclusions and absence of pathologic hallmarks of motor neuron disease. One of the subjects’ clinical presentation was that of FTD and the other was that of progressive supranuclear palsy (19). No neuropathologic information is available on an additional subject, whose clinical presentation was that of primary progressive aphasia and who was alive at the time of the report (12).

Before this study, a clinical presentation consistent with CBS was reported in association with 3 additional PGRN mutations: IVS7+1G>A (p.Val200GlyfsX18), IVS8-1G>C (p.Val279GlyfsX5), and c.813_816delCACT (p.Thr272SerfsX10) (10, 12, 13). The IVS7+1G>A (p.Val200GlyfsX18) mutation was identified in affected individuals from a Canadian family of Chinese origin. The clinical phenotype of the family’s proband, suggestive of right parieto-occipital dysfunction, was associated with right greater than left hemispheric cortical atrophy and hypometabolism, which were more prominent in the posterior regions (13). Similar clinical and neuroimaging findings have been described in 1 affected individual from an Italian family, who was diagnosed with CBS associated with the c.813_816delCACT (p.Thr272SerfsX10) PGRN mutation (10). Features of limb apraxia and/or AHS have been observed in the advanced stage of the disease course in additional subjects with FTLD-U carrying a PGRN mutation, whose initial clinical presentation differed from that of CBS (19, 21, 36). In addition, a study of a large series of FTLD-U cases has shown a marked degree of parietal lobe degeneration in 50% of cases associated with a PGRN mutation [PGRN(+)] and in 17% of cases without a PGRN mutation [PGRN(-)]. A trend for a higher severity of parietal lobe degeneration in PGRN(+) cases compared with the PGRN(-) was also observed (19).

Consistent evidence of the existence of a highly variable and largely overlapping spectrum of clinical presentations associated with PGRN mutations has been collected from the description of numerous cases. In this sense, PGRN(+) FTLD-U presents interesting similarities with MAPT-associated frontotemporal dementia and Parkinsonism linked to chromosome 17 and with the larger category of FTD syndromes (5, 18). This observation stands in contrast with the pathogenic mechanism of the PGRN mutations, which are all thought to lead to neurodegeneration through nonsense mediated decay of the mutant mRNA and haploinsufficiency (16, 17). The proband’s neurologic, neuropsychologic, and neuroimaging presentation shows that PGRN mutations may lead to a neurodegenerative process predominantly involving the parietal lobes in the early disease stage. Remarkably, a higher extent of atrophy and ubiquitin/TDP-43 pathology in the parietal cortex, compared with that of other cortical areas, was found in the proband.
also at the neuropathologic examination. These findings demonstrate that the parietal lobes may constitute the most vulnerable anatomical areas in some cases of PGRN(+)-FTLD-U, therefore, raising questions on the accuracy of the term FTLD to describe these syndromes. The detailed clinical, pathologic, and molecular characterization of cases with peculiar clinical presentations may provide important insights on the neurobiologic base of this heterogeneity.

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