Novel splicing mutation in the progranulin gene causing familial corticobasal syndrome

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Corticobasal syndrome (CBS) is a rare cognitive and movement disorder characterized by asymmetric rigidity, apraxia, alien-limb phenomenon, cortical sensory loss, myoclonus, focal dystonia, and dementia. It occurs along the clinical spectrum of frontotemporal lobar degeneration (FTLD), which has recently been shown to segregate with truncating mutations in progranulin (PGRN), a multifunctional growth factor thought to promote neuronal survival. This study identifies a novel splice donor site mutation in the PGRN gene (IVS7+1G→A) that segregates with CBS in a Canadian family of Chinese origin. We confirmed the absence of the mutant PGRN allele in the RT–PCR product which supports the model of haploinsufficiency for PGRN-linked disease. This report of mutation in the PGRN gene in CBS extends the evidence for genetic and phenotypic heterogeneity in FTLD spectrum disorders.

Keywords: Corticobasal syndrome; frontotemporal lobar degeneration; progranulin; gene; mutation

Abbreviations: CBS = corticobasal syndrome; CBD = corticobasal degeneration; CHMP2B = chromatin-modifying protein 2B; FTD = frontotemporal dementia; FTLD = frontotemporal lobar degeneration; MAPT = microtubule-associated protein tau; PGRN = progranulin; PPA = primary progressive aphasia; PSP = progressive supranuclear palsy; RT-PCR = reverse transcriptase-polymerase chain reaction

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Introduction

In 1967, Rebeiz and colleagues (Rebeiz et al., 1967) described three cases of a progressive, perceptuo-motor disorder characterized by an asymmetric akinetic-rigid syndrome and apraxia. They termed the disorder ‘corticodentatonigral degeneration with neuronal achromasia’ based on identified pathological features. Since then, a variety of terms have been applied to this enigmatic disorder of interest to cognitive and movement disorder neurologists worldwide including corticonigral degeneration with neuronal achromasia, cortical degeneration with swollen chromatolytic neurons, cortical basal ganglionic, corticobasal ganglionic, and the most common designation, corticobasal degeneration (CBD) (reviewed in Mahapatra et al., 2004). This terminology has caused considerable nosological confusion over the years presumably because some terms refer to the underlying pathological changes, while others refer to the neural substrates causing the recognized clinical syndrome.

To add to this nosological uncertainty, extensive research has demonstrated significant clinical and pathological heterogeneity in CBD (reviewed in Boeve et al., 2003; Lang 2003). Specifically, cases presenting with the ‘classical’ clinical syndrome of CBD often have alternative pathologies (i.e. not CBD) underlying the clinical manifestations such as progressive supranuclear palsy (PSP), frontotemporal...
dementia (FTD), Alzheimer’s disease, dementia with Lewy bodies and Creutzfeldt-Jacob disease. Conversely, pathologically confirmed cases of CBD (Dickson et al., 2002) may present with a variety of clinical phenotypes in addition to ‘classical’ CBD including primary progressive aphasia (PPA) and FTD. As a result, it has been suggested that the term corticobasal syndrome (CBS) be applied to clinically diagnosed cases presenting with the ‘classical’ features of asymmetric rigidity, apraxia, alien-limb phenomenon, cortical sensory loss, myoclonus, and focal dystonia (Kertesz et al., 2000a; Boeve et al., 2003; Lang, 2003; Litvan et al., 2003). Herein, we use the term CBS to refer to clinically diagnosed cases without proof of typical CBD pathology conforming to the clinical diagnostic criteria (Boeve et al., 2003). Included in this syndromic definition are patients presenting with early dementia, for which there is evidence suggesting this to be the most common initial presentation (Bergeron et al., 1998; Grimes et al., 1999b; Mathuranath et al., 2000). The cognitive symptoms and underlying pathologies of CBS have many overlapping features with those of FTD prompting current nosological classification to include CBS as part of the spectrum of FTD (Kertesz et al., 2000b; Neary et al., 1998; Josephs et al., 2006). Similar to CBS, several terms have been applied to describe this heterogeneous disorder including FTD/Pick complex (Kertesz, 2003), frontotemporal lobar degeneration (FTLD) (Neary et al., 1998), Pick’s disease (Pick, 1892), and FTD (The Lund and Manchester Groups, 1994). We have adopted the term FTLD in this paper.

FTLD encompasses a wide spectrum of clinical entities ranging from FTD, PPA, semantic dementia, CBS, PSP, FTD-motoneuron disease (FTD-MND) and FTD with parkinsonism linked to chromosome 17 (FTDP-17) (Kertesz, 2003, 2005). It represents a group of primary degenerative dementias with predominant frontal and/or temporal lobe symptoms (e.g. decline in social and personal behaviour, apraxia, stereotyped behaviour, hyperorality and aphasia) (Kertesz, 2005) and consensus diagnostic and neuropathological criteria have been proposed (Neary et al., 1998; McKhann et al., 2001). The neuropathological characteristics of FTLD include variable frontal and temporal and basal ganglia atrophy with neuronal loss and gliosis (with tau or ubiquitinated inclusions). The deposition and abnormal processing of tau encoded by the gene named microtubule-associated protein tau (MAPT) play an important role in the development of several forms of FTLD, including CBS (Goedert et al., 2000; Hutton 2001; McKhann et al., 2001). However, up to 60% of FTLD cases lack tau-positive neuronal inclusions, primarily displaying a microvacuolization of the superficial neuropil in the cortex (often with ubiquitin-positive inclusions in cortical neurons) (Kertesz et al., 2000a; Ince and Morris, 2006).

FTLD is a genetically complex disorder with at least three known causal genes. The aberrant splicing mutation in chromatin-modifying protein 2B (CHMP2B) is responsible for autosomal dominant FTLD in a large Danish family (Skibinski et al., 2005). However, the CHMP2B is not a common cause of FTLD since several large series of FTLD patients failed to detect any CHMP2B mutations (Cannon et al., 2006; Momeni et al., 2006). Many of the autosomal dominant FTDP-17 families are explained by mutations in the MAPT gene (Hutton et al., 1998; Poorkaj et al., 1998; Spillantini et al., 1998). However, in several FTLD families linked to chromosome 17q21, MAPT mutations were excluded. Recently the disease in many of these families was explained by truncating mutations in the progranulin (PGRN) gene which was mapped ~1.7 Mb centromeric of the MAPT locus (Baker et al., 2006; Cruts et al., 2006). The PGRN gene encodes a secreted multifunctional growth factor involved in development, wound repair and inflammation. Patients with PGRN mutations do not have tau pathology. Instead there are ubiquitin-immunoreactive neuronal cytoplasmic and intraneuronal inclusions, the protein identity of which remains unknown (Baker et al., 2006; Cruts et al., 2006; Mackenzie et al., 2006). Neurodegeneration in mutation carriers is caused by PGRN haploinsufficiency due to nonsense-mediated decay since transcript analysis demonstrated the absence of the mutant allele.

Herein, we describe the clinical, neuropathological and genetic findings of a CBS-like disease which is segregating a novel PGRN mutation in a Canadian family of Chinese origin. This finding extends knowledge on the clinical, pathological and genetic heterogeneity of CBS and FTLD.

**Material and methods**

**Subjects**

The proband (Case 4150) was recruited through the Linda C. Campbell Cognitive Neurology Research Unit at Sunnybrook Health Sciences Centre in Toronto as part of the Sunnybrook Dementia Study. This is a prospective, longitudinal study of dementia and ageing with well over 800 subjects enrolled to date approved by the local Research Ethics Boards. Patients or their substitute decision makers provide written, informed consent to participate in accordance with the Declaration of Helsinki. The proband underwent a detailed clinical evaluation including: history and physical examination, and standardized behavioural neurology assessment. Routine biochemical screening was done to exclude any other causes for their presentation. The patient was seen every 6 months for routine clinical follow-up and had yearly prospective longitudinal assessments which included: detailed neuropsychological battery (measures of general intelligence and cognition, language, praxis, visuospatial ability, attention and working memory, and executive functions), measures of neuropsychiatric symptoms and of functional status. Structural and functional neuroimaging of the brain with MRI and single photon emission computed tomography (SPECT), respectively, were performed.

The sister of the proband (Case 4993) was identified through clinical history from the proband. Information pertaining to this case is limited to that ascertained through a telephone interview with her caregiver and through an autopsy report as this patient was residing out of country. The normal control group consisted of 200 unrelated subjects of North American origin (mean age at time of examination of 72.7 ± 8.4 years).
Neuropathology
Neuropathological examination was carried out by two of the authors (R.H., J.B.). Paraffin-embedded sections were stained with haematoxylin and eosin, Luxol fast blue (LFB), Bielschowski and Gallyas. Immunostains using commercial antibodies for tau (Dako, A0024) and ubiquitin (Vector Labs, ZPU576) were performed.

Genetic analysis
Genomic DNA and RNA were extracted from whole blood using Qiagen kits. Two affected members of the family (Case 4150 and Case 4993) were tested for mutations in exons 1 and 9–13 of the MAPT gene by direct sequencing as previously described (Kertesz et al., 2000a). The entire open reading frame with the exon-intron boundaries of the CHMP2B and PGRN genes was sequenced in both affected individuals as previously described (Baker et al., 2006; Skibinski et al., 2005). RT–PCR primers were designed for PGRN exon 3 (5′-GCCACTCCTGCATCTTTACC-3′) and exon 8 (5′-TTTTCTTTGAGAGACCTTT-3′). The RT–PCR conditions were 94°C for 5 min, followed by 40 cycles of 94°C for 30 s, 58°C for 30 s, 72°C for 30 s, and 7 min at 72°C. Mutations were detected by direct inspection of the fluorescent chromatographs and by analysis using the SeqScape software version 1.0 (Applied Biosystems, Foster City, CA).

Results
Clinical features and autopsy results
This family of Chinese origin presented with inheritance of a progressive neurodegenerative disorder characterized by dementia and motor decline, including rigidity, dystonia, apraxia, cortical sensory loss, visuospatial dysfunction and behavioural changes (Fig. 1A). Family records indicate that

![Fig. 1](A) The pedigree structure of the Canadian family showing the inheritance of the disease (with age at onset). Affected individuals are shown as filled symbols and the arrow points to the proband. The gender of the individuals has been masked to protect family confidentiality. (B) Genomic DNA (gDNA) and RT–PCR (cDNA) sequence fluorescent chromatograms around the PGRN mutation (IVS7+1G→A) observed in the patients and the sequence around common synonymous variation rs25646; (C) An agarose gel photograph of the PGRN product from RT–PCR, using RNA obtained from white blood cells of the affected family member (4150) and normal control (the 586 bp band corresponds to the PGRN fragment containing exons 3–8 confirmed by sequencing analysis).
two out of 12 siblings have been affected with corticobasal syndrome. A third family member has developed early Parkinsonism. Two patients were available for the genetic and clinical study.

**Case 4150 (proband)**

This 71 year old right-handed woman with a previous history of hyperthyroidism treated with radioablation and requiring thyroid replacement presented at age 62 with the insidious onset of behavioural changes including increased irritability, depression, social withdrawal and suspiciousness. Subsequently, she began to experience difficulties with short-term memory, planning, attention, word-finding difficulties and getting lost in familiar environments. Abnormalities on her initial examination (age 65) were a left visual field defect which was thought to be, in part, secondary to profound left hemi-neglect, left cortical sensory loss (specifically, sensory extinction and agraphesthesia), left-hand ideomotor apraxia and a dressing apraxia. These exam features are consistent with right parieto-occipital dysfunction. She scored 20/30 on the Mini-Mental Status Examination (MMSE) putting her in the moderate range of dementia severity. Cognitive testing confirmed severe visual perceptual dysfunction and also revealed short-term memory deficits, impaired executive functions, anomic aphasia and apraxia. The results of the neuropsychological battery and standardized scores are summarized in Table 1. An MRI of the brain revealed right greater than left hemispheric cortical atrophy and ventricular dilatation, slightly more prominent in the posterior regions; there were also some periventricular white matter changes (Fig. 2A). A brain SPECT scan demonstrated a large right parieto-occipital perfusion deficit extending into the temporal and frontal regions with a milder decrease in perfusion in the left parietal lobe (Fig. 2B). The neuropsychological data was collected within a 1 month time period of the MRI and SPECT images. The provisional diagnosis was thought to be posterior cortical atrophy, a possible

<table>
<thead>
<tr>
<th>Demographics, neuropsychological battery and functional measures (test name/maximum raw score)</th>
<th>Raw scores for Case no. 4150</th>
<th>Standardized score</th>
<th>Category</th>
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<tbody>
<tr>
<td>Age of onset</td>
<td>62</td>
<td>—</td>
<td>—</td>
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<tr>
<td>Age at this testing</td>
<td>65</td>
<td>—</td>
<td>—</td>
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<tr>
<td>Duration of disease at testing</td>
<td>3</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Years of education</td>
<td>12</td>
<td>—</td>
<td>—</td>
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<tr>
<td>General cognition</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Folstein’s Mini-Mental Status Examination/30</td>
<td>20</td>
<td>≥28 (NCO)</td>
<td>Impaired</td>
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<tr>
<td>Mattis Dementia Rating Scale/144</td>
<td>92</td>
<td>2 (SS)</td>
<td>Impaired</td>
</tr>
<tr>
<td>Memory</td>
<td></td>
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<tr>
<td>California Verbal Learning Test—long delay free recall/16</td>
<td>4</td>
<td>−2 (ZS)</td>
<td>Impaired</td>
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<tr>
<td>Delayed visual reproduction/41</td>
<td>0</td>
<td>1st percentile</td>
<td>Impaired</td>
</tr>
<tr>
<td>Language</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Western Aphasia Battery—total/100</td>
<td>83</td>
<td>−2 (ZS)</td>
<td>Impaired</td>
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<tr>
<td>Western Aphasia Battery—comprehension/10</td>
<td>8</td>
<td>−2 (ZS)</td>
<td>Impaired</td>
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<tr>
<td>Boston naming/30</td>
<td>19</td>
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<td>Impaired</td>
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<tr>
<td>Semantic fluency/20</td>
<td>6</td>
<td>&lt;10th percentile</td>
<td>Borderline-impaired</td>
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<tr>
<td>Praxis</td>
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<td></td>
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<tr>
<td>Western Aphasia Battery—praxis/60</td>
<td>48</td>
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<td>Attention and working memory</td>
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<tr>
<td>Digit span—forward/12</td>
<td>6</td>
<td>30th percentile</td>
<td>Normal</td>
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<tr>
<td>Digit span—backward/12</td>
<td>2</td>
<td>5th percentile</td>
<td>Borderline</td>
</tr>
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<td>Visuospatial abilities</td>
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<tr>
<td>Rey Osterrieth complex figure—copy/36</td>
<td>0</td>
<td>&lt;1st percentile</td>
<td>Impaired</td>
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<tr>
<td>Benton line orientation/30</td>
<td>N/A</td>
<td>≤4 (SS)</td>
<td>Impaired</td>
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<tr>
<td>Executive functions</td>
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<td></td>
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<tr>
<td>Phonemic fluency (F-, A-, S-words)</td>
<td>16</td>
<td>3 (SS)</td>
<td>Impaired</td>
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<tr>
<td>Wisconsin Card Sort Test—categories/6</td>
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<td>Impaired</td>
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<tr>
<td>Wisconsin Card Sort Test—perseverative errors</td>
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<td>Impaired</td>
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<td>Activities of daily living</td>
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<td></td>
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<tr>
<td>Disability assessment for dementia (%)</td>
<td>53</td>
<td>100 (NCO)</td>
<td>Impaired</td>
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<tr>
<td>Neuropsychiatric symptoms</td>
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<td></td>
<td></td>
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<tr>
<td>Neuropsychiatric inventory—total/144</td>
<td>24</td>
<td>0 (NCO)</td>
<td>Abnormal</td>
</tr>
<tr>
<td>Neuropsychiatric inventory—apathy/12</td>
<td>8</td>
<td>0 (NCO)</td>
<td>Abnormal</td>
</tr>
<tr>
<td>Neuropsychiatric inventory—depression/12</td>
<td>8</td>
<td>0 (NCO)</td>
<td>Abnormal</td>
</tr>
<tr>
<td>Neuropsychiatric inventory—disinhibition/12</td>
<td>0</td>
<td>0 (NCO)</td>
<td>Normal</td>
</tr>
<tr>
<td>Cornell Depression Scale (%)</td>
<td>53</td>
<td>&lt;25 (NCO)</td>
<td>Depressed</td>
</tr>
</tbody>
</table>

*Abbreviations: NCO = normal cut-off; SS = scaled score (mean = 10; 1 SD = 3); ZS = Z-score; N/A = not assessable.*
variant of Alzheimer’s disease. She was initiated on a cholinesterase inhibitor with no major change in symptoms apart from some improvement in attention.

A year after her initial assessment (age 66), the patient’s cognitive performance continued to decline (MMSE = 12) and she required assistance in all activities of daily living. She also was developing an asymmetric akinetic-rigid syndrome including prominent rigidity of the left upper and lower extremities, bradykinesia and a stooped posture with a shuffling gait. The provisional diagnosis was changed to CBS based on the emergence of an asymmetric akinetic-rigid syndrome and severe left-sided ideomotor apraxia. She met clinical criteria for CBS (Boeve et al., 2003). Over the next 3 months, the patient became verbally and physically aggressive towards her daytime caregiver. Cognitively, her dementia had progressed into the severe range and she was completely dependent for self care. She had a positive glabellar tap and bilateral grasp reflexes consistent with frontal release phenomena. At this point, she was observed to be constantly biting her finger nails, likely representing repetitive, stereotyped behaviour. Clinically, her akinetic-rigid syndrome had progressed and she now developed dystonic posturing of her left hand, and worsening left-sided apraxia, the combination of which produced a useless left arm.

Approximately 3 years after her initial assessment (age 68), she lost the ability to ambulate and developed corticospinal tract findings on the left side of her body (i.e. left hyperreflexia and extensor plantar response). Her verbal output declined and she would often repeat phrases such as ‘you’re killing me’. She continued to decline and 4 years after the initial assessment (age 69), her speech output diminished to the point where she was only able to grunt to indicate her needs, with relative preservation of verbal comprehension. Eventually, she became mute and lost the ability to comprehend and interact with others. Recently, she developed dysphagia to liquids and is able to eat only pureed foods. Currently (age 71), she is bed-bound with end-stage CBS about 9 years into the course of her illness.

**Case 4993 (sister of proband)**

This deceased 61-year-old woman had a history of dementia and motor decline since age 57 consisting of axial and extremity rigidity and aphasia. She had significant contractures and flexion posturing of her upper extremities and right lower extremity. She required complete personal care and gastrostomy tube feeds for nutrition towards the end of her disease course. Her clinical diagnosis by a neurologist was CBS. She passed away at age 61 from medical
Neuropathology (case 4993)

Gross: The whole brain weighed 940 g unfixed. Examination of the right half of the fixed brain demonstrated mild to moderate sulcal widening in the frontotemporal regions. Coronal sections showed a well-defined and regular cortical ribbon without focal defects. Significant widening of the circular sulcus and Sylvian fissure was noted. The caudate nucleus and putamen were atrophic. The hippocampus was normal in size. The substantia nigra was normally pigmented. There were no gross abnormalities of the cerebellum, pons, medulla or cervical spinal cord.

Microscopic: Severe pancortical micro-vacuolation associated with neuronal loss and gliosis was seen in the frontal cortex. Similar changes were seen in the insular and temporal cortices and in the basal ganglia. The vacuoles varied in size and were more numerous in the superficial layers of the cortex. Vacuoles were not encountered in the thalamus, brainstem, cerebellum and spinal cord. The vacuoles were located within neuronal cytoplasm and the neuropil. Patchy myelin pallor was demonstrated in the white matter underlying the atrophic cortical areas. This finding was best seen in LFB stains. The hippocampus was well-preserved. There was some neuronal loss in the substantia nigra with an absence of Lewy bodies in the brainstem or cerebral cortex. Bunina bodies were not seen in the motor nuclei of the cranial nerves. Bielschowski stains demonstrated no neocortical senile plaques but rare, probably age-related, plaques were identified in the hippocampus. No astrocytic plaques were observed in Gallyas stains. There were no axonal spheroids. Immunostains for tau protein were performed and showed no reactivity in neurons or other cells. Immunostains for ubiquitin demonstrated ubiquitin-reactive neuronal cytoplasmic inclusions. Ubiquitin-reactive neuronal intranuclear inclusions were also observed occasionally. Scattered neurites in the frontotemporal cortex were also ubiquitin-positive. These findings are compatible with the diagnosis of FTD with ubiquitin-only positive inclusions or FTD-U pathology (Mann et al., 2000; Lipton et al., 2004; Taniguchi et al., 2004; Mackenzie and Feldman 2005).

The third affected family member (brother of proband), after retiring at age 65, experienced ‘dizzy’ spells and did not feel well. He was assessed by a movement disorder specialist and was diagnosed with early Parkinson’s disease. Although he was never diagnosed with a concurrent dementing illness, he has been unable to drive or prepare meals for himself. Information pertaining to this brother was limited to history from a family member. There was no history of dementia or parkinsonism in either parent. The father died in his sixties from tuberculosis. The mother died at age 65 from ‘pulmonary edema’. The other siblings are unaffected.

Genetic analysis

Due to the clinical course and strong family history of disease, we performed mutation analysis of all three known FTLD genes (MAPT, CHMP2B and PGRN) for Patients 4150 and 4993. We did not observe any sequence variations in the MAPT and CHMP2B genes. However, in the PGRN gene we identified a novel heterozygous single nucleotide G→A mutation in the invariant ‘GT’ splice donor site 3′ of exon 7 (genomic position 5680; Accession Number AC003043) (Fig. 1B). The exon numbering was according to the National Center for Biotechnology Information (http://www.ncbi.nlm.nih.gov/) and our exon 7 corresponds to exon 6 in the published report (Baker et al., 2006). The IVS7+1G→A mutation segregates with the disease in the two affected family members (4150 and 4993) and was not found in 200 normal controls.

The mutation is predicted to have dramatic consequences on the maturation process of PGRN mRNA leading to the removal of exon 7 which would create a frame shift and truncate the protein to half its normal length (amino acid position 236). Likely such a transcript will be destroyed by nonsense-mediated decay. In agreement with this, the result of the RT–PCR, using RNA isolated from the white blood cells of Patient 4150, revealed only the wildtype product on agarose gel (Fig. 1C). The specificity of this RT–PCR product, containing exons 3–8 of the PGRN gene, was confirmed by direct sequencing analysis. Importantly, this patient, who is heterozygous (T→C) for a common synonymous polymorphism in exon 5 (D128D; rs25646) using genomic DNA, showed only the ‘C’ allele in the RT–PCR product (Fig. 2B). Hence, the RT–PCR result demonstrates the absence of the mutant PGRN transcript.

Discussion

In the family reported here, the novel splice donor site mutation in the PGRN gene (IVS7+1G→A) affects the sequence that is important in the recognition of the intron/exon boundary and removal of the intron (Berget, 1995). There are no doubts about the pathological nature of this mutation. It segregates with the disease in two affected family members and was absent in 200 unrelated normal controls. The predicted consequence of the splicing mutation is either the expression of the truncated protein or the haploinsufficiency of PGRN due to nonsense-mediated decay. According to the published reports the second possibility is more likely (Baker et al., 2006; Cruts et al., 2006). Indeed, our attempt to evaluate the pathological consequences of the IVS7+1G→A mutation by RT–PCR using RNA from the blood cells of Patient 4150 did not identify aberrant PGRN transcripts (Fig. 1C). Instead we confirmed the absence of the mutant PGRN allele in the RT–PCR product (Fig. 1B). Hence, the progression from normal function to the disease state would result from the reduction of the PGRN level, further supporting the model of haploinsufficiency for PGRN-linked FTLD.
Previously, a different splicing mutation (named IVS8+1G→A) was reported in one family; however, a source of RNA was not available to confirm the haploinsufficiency mechanism (Baker et al., 2006).

The cases described in this family met clinical criteria for CBS (Boeve et al., 2003). Pathology in one affected individual demonstrated ubiquitin-positive, tau-negative cytoplasmic and intranuclear inclusions consistent with the pathology reported in the original FTLD families in which PGRN mutations co-segregate with disease (Baker et al., 2006; Cruts et al., 2006). To our knowledge, this is the first report of mutation in PGRN causing familial CBS with underlying FTD-U inclusion pathology. This type of pathology has been demonstrated previously in sporadic cases of CBS (Grimes et al., 1999a; Kertesz et al., 2005). One could surmise that these previously reported ‘sporadic’ cases may come from families with PGRN mutations that were non-penetrant.

Previous familial studies have demonstrated that CBS coexists with PSP, and/or FTLD (Brown et al., 1996, 1998; Gallien et al., 1998; Bugiani et al., 1999; Tuite et al., 2005; Boeve et al., 2002; Uchihara and Nakayama, 2006). Only two of these studies had more than one affected individual with CBS making this a relatively uncommon presentation in FTLD families (Tuite et al., 2005; Uchihara and Nakayama, 2006). Our study extends this literature in that two of the affected family members have CBS, while one has early parkinsonism which may be evolving into a dementing condition based on history. Perhaps, the novel splice donor site mutation in PGRN identified in this family predicts the phenotypic expression of CBS as opposed to FTLD or PSP. However, this would be unlikely given the current haploinsufficiency model proposed for PGRN mutation. Another possibility may be that the FTLD phenotype may be differentially expressed in Asians such that CBS is more likely to occur. Reasons for this might include epigenetic factors, modifier genes and/or environmental influences that ‘tip the balance’ in favour of one particular manifestation of FTLD over another.

The proband in our study presented initially with behavioural symptoms consisting of increased irritability, depression, social withdrawal, and suspiciousness. Prominent visuospatial dysfunction was present early on in the clinical course. Subsequently, she had difficulties with short-term memory, executive functions and language. MRI and SPECT imaging of the brain (Figs 2A and B) demonstrated cortical atrophy and reduced perfusion, respectively, in the right parieto-occipital greater than right frontotemporal regions which was clearly asymmetrical when compared with the left hemisphere. This suggested an initial diagnosis of posterior cortical atrophy although clinically through neuropsychological testing there were also deficits of anterior cerebral dysfunction. Once the extrapyramidal features evolved, the diagnosis of CBS became clear.

We have previously reported a case of a patient with sporadic CBS who presented initially with prominent visuospatial dysfunction and a semi-neglect syndrome similar to the proband in the current study (Kleiner-Fisman et al., 2003). Interestingly, final pathological diagnosis in this patient confirmed ubiquitin-positive, tau-negative cytoplasmic and intranuclear inclusions consistent with FTD-U inclusion pathology (J. Bilbao, unpublished data) similar to the pathology observed in the current study. Visuospatial dysfunction in CBS has also been observed rarely (Mendez 2000; Okuda et al., 2000) with one study demonstrating underlying typical CBD pathology (Tang-Wai et al., 2003). Therefore, CBS presenting with prominent visuospatial dysfunction does not necessarily predict the specific underlying pathological diagnosis.

Although both cases described in this family were diagnosed with CBS, there were significant differences in their clinical course. The proband presented at age 62 with behavioural symptoms and posterior cerebral dysfunction and evolved over a few years into CBS and is still living 9 years after disease onset, although nearing end-stage disease. The sister of the proband presented at a younger age (57 years) and had early and prominent motor features which eventually led to death at age 61, 4 years after symptom onset. Unknown environmental or genetic factors or stochastic events must contribute to this variability in age of onset and disease severity within families and will require further investigation.

Clinical diagnosis along the FTLD spectrum is challenging and frequently longitudinal follow-up of patients is required to ascertain the most likely provisional diagnoses. Take, for example, the prospective, clinic-based cohort of FTLD patients of Kertesz et al. (2005) that was followed longitudinally to autopsy. In this cohort, the authors describe patients presenting with initial syndromes ranging from behavioural variants of FTLD, CBS, PSP, to PPA. The majority of these patients then went on to develop second and not uncommonly third syndromes with significant clinical overlap along the FTLD spectrum. Added to this complexity is the fact that there were a variety of pathologies underlying each of the clinical phenotypes ranging from tau-positive to tau-negative types. For the most part, the clinical syndrome of FTLD observed is dependent more on ‘the distribution of the underlying pathological state rather than on its nature’ (Lang, 2003). As we learn more about the underlying molecular pathogenic mechanisms of FTLD spectrum disorders, diagnostic accuracy in life will improve and this will also lead to potential therapies to prevent or cure these debilitating disorders.

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