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NOVEL GRN MUTATION PRESENTING AS AN APHASIC DEMENTIA AND EVOLVING INTO CORTICOBASAL SYNDROME

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Mutations in the granulin (*GRN*) gene on chromosome 17 most commonly result in behavioral variant frontotemporal dementia (FTD) or primary progressive aphasia (PPA), although a wide range of phenotypes have been described.[1,2] At the time of publication, 172 mutations have been described (molgen.vib-ua.be/FTDMutations), 79 of which are thought to be pathogenic, with no clear genotype-phenotype correlation. Here, we describe a novel mutation presenting as a dysexecutive, aphasic dementia and evolving into a corticobasal syndrome (CBS) phenotype.

Case report. A 61-year-old right-handed woman presented with difficulty expressing herself in writing more so than speech. Her problems started around the age of 60, with deterioration of her penmanship. This was followed by difficulty with simple arithmetic, impairing her ability to work, as well as trouble with tasks reliant on sequencing, such as preparing a sandwich or making coffee. Closer to the time of evaluation, the patient and her family noticed word finding difficulty, yes-no confusion, word substitutions from semantically related categories, and mild gait imbalance.

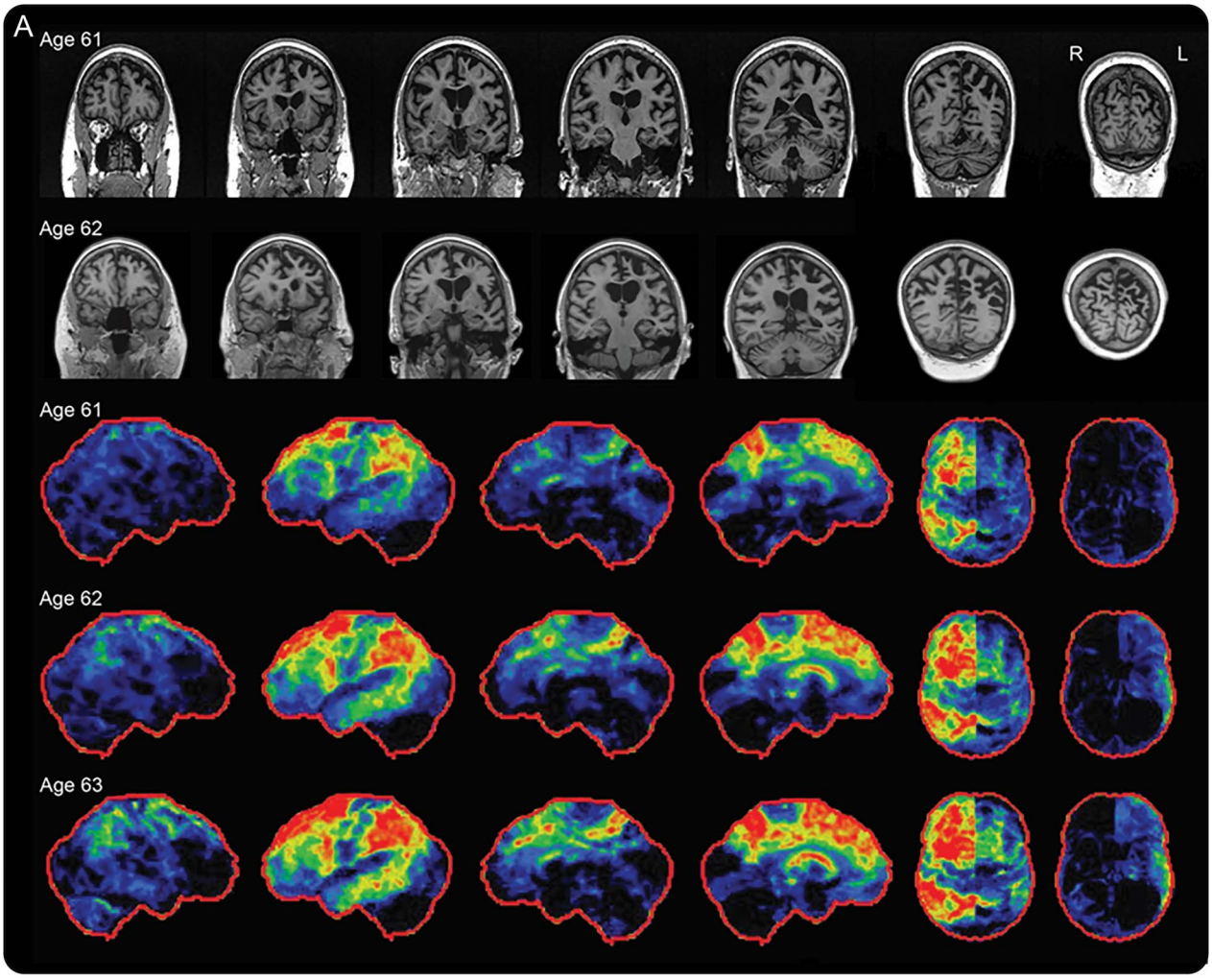
Her initial cognitive evaluation revealed deficits in calculation and digit span, but no trouble with naming, recall, registration, or construction. Her repetition was spared, but she had difficulty following 3 step commands, and her writing was considerably impaired. She had clear left hemispheric atrophy and hypometabolism (figure 1A) and was amyloid-PET negative. Formal neuropsychometric testing 18 months after symptom onset demonstrated impaired executive, letter/category fluency, and visuospatial skills (figure 1B). Over the following year, she developed more generalized cognitive, language, and motor impairment. She had right hemibody parkinsonism on examination and met the criteria for CBS during her second visit at age 62.[3] At her last follow-up at age 63, she had minimal meaningful language output and little use of her right upper extremity, which was held in a flexed posture with marked rigidity. She had minimal behavioral disturbance and was still able to sing, despite being essentially nonverbal in conversation.

Her family history was notable for Parkinson disease and dementia (figure 2). Genetic testing was offered in light of the positive family history (Goldman score 2).[4] Full sequencing of the *GRN* gene revealed a previously unreported mutation in exon 12 (c.1535delC, Pro512LeufsX5), resulting in a premature stop codon. Both *MAPT* sequencing and molecular analysis of the *C9orf72* gene were normal. Plasma progranulin levels were quantified and compared with subjects with known pathogenic mutations as well as controls (figure 1C). Controls had levels more than double that of known mutation carriers. The level in our case was far below than that seen in controls, albeit slightly higher than other known mutation carriers, supporting the pathogenicity of the mutation.

Discussion. It has been a little more than a decade since the first report linking mutations in the *GRN* gene to cases of tau-negative familial FTD was presented.[2,5] Despite important advances in our understanding of the role granulin plays in the nervous system, including as a growth factor and modulator of inflammation, the exact mechanism by which the haploinsufficiency that results from mutations causes neurodegeneration has not been elucidated.

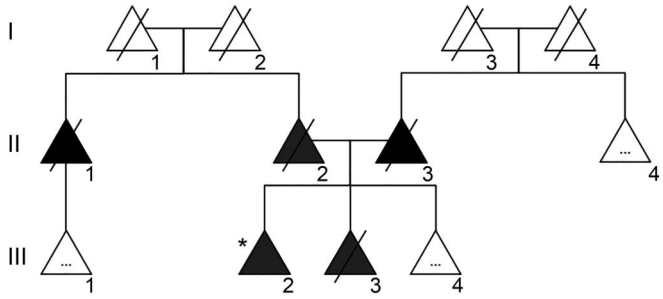
Our case better illustrates the heterogeneity in *GRN*-related disease. Although related to a novel mutation in exon 12, a relatively rare site for *GRN* mutations, her presentation shares features of previously reported mutations. Her initial complaint of deteriorating penmanship was likely due to apraxic agraphia, well reported in CBS, but reported only once in *GRN*-related CBS previously.[6] Her phenotype at the time of initial evaluation did not qualify for a diagnosis of PPA based on her impairment in nonlanguage domains, but the prominent language difficulty is in keeping with PPA being the second most common presentation of *GRN* mutations and a common early feature in CBS.[1,7] Over time, a clear CBS picture emerged, another common manifestation of *GRN* mutations.[1,7] Her prominent parkinsonism, including marked rigidity, raises the possibility

Figure 1 **Results of imaging, neuropsychological and molecular analyses**



(A) MRI (rows 1 and 2) and FDG-PET (rows 3–5) findings at presentation (age 61 years) and follow-up (ages 62 and 63 years). Note moderate-to-severe, asymmetric left frontal-temporal-parietal atrophy, with progression at follow-up, and relative hippocampal sparing. The same pattern is present on fludeoxyglucose PET (FDG-PET) imaging, with almost exclusively left-sided hypometabolism even at follow-up, and little-to-no anterior and medial temporal involvement. (B) Performance on key tests in the neuropsychological battery is shown graphically, with performance on each test displayed using the Mayo Older American Normative Studies (MOANS) standard score as reference. Scores at or below 6 are usually considered abnormal. Impaired performance was found on fluency measures, attention/executing control measures, and one of the visuospatial measures. (C) Plasma progranulin levels quantified by ELISA in controls (CN) and affected mutation carriers (*GRN*+). Values in CN (mean 46.53 ng/mL, SD 3.9 ng/mL) were significantly higher than those in *GRN*+ (mean 14.48 ng/mL, SD 1.38 ng/mL). The level in our case (23.9 ng/mL) is shown in red. AVLT = Auditory Verbal Learning Test; BNT = Boston Naming Test; CF = category fluency; DRS-2 = Dementia Rating Scale 2; *GRN*+ = *progranulin* mutation cases; JLO = judgment of line orientation; L = left; LF = letter fluency; R = right; TMT A = Trial Making Task Part A; TMT B = Trial Making Task Part B; WAIS-BD = Wechsler Adult Intelligence Scale Block Design; WAIS-DS = Wechsler Adult Intelligence Scale Digit Span; WMS-R LM = Wechsler Memory Scale-Revised Logical Memory.

Figure 2 **Outline of family pedigree**



Triangles represent individuals, and shaded triangles represent individuals affected by a degenerative disease. Triangles with diagonal lines through them represent deceased individuals. The proband is indicated by an asterisk. An elipsis in a triangle represents multiple unaffected offspring not shown to maintain confidentiality. One parent was diagnosed with Parkinson disease (II.2) and the other with dementia (II.3), both late in life. A sibling of the parent with dementia was diagnosed with Alzheimer disease dementia late in life (II.1). One of the patient's siblings was suspected elsewhere to have Pick disease (III.3), based on behavioral disturbance, aphasia, and cognitive impairment, and this person passed away in the early 60s. No postmortem examination was performed. Multiple other siblings were cognitively normal (all older than 45 years).

that the family member with parkinsonism may in fact have carried the same mutation. Although no imaging features are pathognomonic, *GRN* mutations tend to cause more asymmetric atrophy and hypometabolism than is seen in sporadic FTD or in *MAPT* or *C9orf72* mutations, as well as more parietal involvement and higher rates of atrophy.[7–9] The reasons for the asymmetry, particularly marked in our case, remain a mystery, especially in light of the fact that the haploinsufficiency would be thought to affect both hemispheres to a similar degree.

Our case illustrates the importance of considering *GRN* mutations in cases with markedly asymmetric involvement and a positive family history for dementia or parkinsonism.

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