Progranulin Mutations as Risk Factors for Alzheimer Disease

David C. Perry, MD; Manja Lehmann, PhD; Jennifer S. Yokoyama, PhD; Anna Karydas, BA; Jason JiYong Lee, BS; Giovanni Coppola, MD; Lea T. Grinberg, MD, PhD; Dan Geschwind, MD, PhD; William W. Seeley, MD; Bruce L. Miller, MD; Howard Rosen, MD; Gil Rabinovici, MD

Importance: Mutations in the progranulin gene are known to cause diverse clinical syndromes, all attributed to frontotemporal lobar degeneration. We describe 2 patients with progranulin gene mutations and evidence of Alzheimer disease (AD) pathology. We also conducted a literature review.

Observations: This study focused on case reports of 2 unrelated patients with progranulin mutations at the University of California, San Francisco, Memory and Aging Center. One patient presented at age 65 years with a clinical syndrome suggestive of AD and showed evidence of amyloid aggregation on positron emission tomography. Another patient presented at age 54 years with logopenic progressive aphasia and, at autopsy, showed both frontotemporal lobar degeneration with TDP-43 inclusions and AD.

Conclusions and Relevance: In addition to autosomal-dominant frontotemporal lobar degeneration, mutations in the progranulin gene may be a risk factor for AD clinical phenotypes and neuropathology.


One of the challenges facing clinicians who evaluate patients with dementia is determining what clinical syndrome best fits with the patient’s presentation and then predicting the most likely underlying molecular pathology. While clinical syndromes often help with this prediction, there is still variability between syndrome and pathology. The term frontotemporal dementia (FTD) refers to a heterogeneous group of clinical syndromes featuring changes in personality, behavior, or language. Frontotemporal lobar degeneration (FTLD) refers to a collection of pathologic diagnoses that can cause these clinical syndromes. Three major genes have been implicated in autosomal-dominant FTD: microtubule associated protein tau (MAPT), progranulin (GRN), and chromosome 9 open reading frame 72 (C9orf72). While mutations in GRN have been described as causing a variety of clinical syndromes, including one suggesting Alzheimer disease (AD), it is thought these various presentations all result from TAR DNA-binding protein 43 (TDP-43) pathology. Here we present 2 patients who suggest GRN mutations may also be risk factors for AD pathology.

Report of Cases

Case 1

A 65-year-old right-handed man presented with 3 years of slowly progressive cognitive changes. His first symptom was misplacing personal items. He retired and attempted to move his office into his home but ultimately left everything packed in boxes on the floor. Subsequently, he had several minor motor vehicle accidents and exhibited poor financial judgment, borrowing up to $150,000 and forgetting to file his taxes. His memory for recent events became impaired, and he developed word-finding difficulties. He angered more easily and compulsively checked door locks. There was no behavioral disinhibition, apathy, loss of empathy, or change in food preferences.

On examination, he asked repetitive questions, was suspicious of the examiner, and made phonemic paraphasic errors in speech. He had mild bilateral agraphasia. He scored 17 of 30 on the Mini-Mental State Examination. Detailed neuropsychological testing revealed significant memory and executive dysfunction. MRI and SPECT scans showed mild atrophy and frontal lobe hypoperfusion, respectively. He was started on donepezil and memantine and continues to receive behavioral therapy.

Author Affiliations: Department of Neurology, University of California, San Francisco (Drs Perry, Lehmann, Yokoyama, Grinberg, Seeley, Miller, Rosen, and Rabinovici, and Ms Karydas); and Departments of Psychiatry and Neurology, Semel Institute for Neuroscience and Human Behavior, University of California, Los Angeles (Mr Lee and Drs Coppola and Geschwind).
logic testing revealed poor verbal and visual memory, confrontational naming, and executive function with relative preservation of visuospatial skills (Table).

Voxel-based morphometry was performed on the patient’s 3-T magnetic resonance imaging scan using SPM version 8 (http://www.fil.ion.ucl.ac.uk/spm/). Preprocessing included segmentation into gray and white matter, alignment and warping with DARTEL, normalization to Montreal Neurological Institute space, modulation, and smoothing with an 8-mm full-width at half maximum Gaussian kernel. Single-subject voxel-based morphometry of combined gray and white matter segmentations was compared with 30 healthy control subjects matched for sex, age, and scanner. Age and total intracranial volume were included as covariates in the regression. Results, displayed in Figure 1A at a threshold of $P < 0.05$ (uncorrected), showed atrophy of medial and lateral temporal and parietal lobes, right greater than left. Based on his clinical presentation, neuropsychologic testing, and imaging, he was diagnosed as having AD.

Positron emission tomography (PET) with the $\beta$-amyloid ($\beta$-A) tracer Pittsburgh Compound B was positive for cortical tracer binding, and PET with fluorodeoxyglucose showed hypometabolism in the bilateral temporoparietal cortex (Figure 2).

The patient had a family history of FTD in 3 maternal relatives. His father had late-life dementia and paternal grandmother had been diagnosed as having AD. Genetic testing revealed that the patient carried the same novel mutation in GRN as his affected maternal family members, an octanucleotide insertion in the coding region (c.1263_1264insGACGGAG) causing frameshift and a premature stop codon, predicted to result in nonsense-mediated messenger RNA decay. His apolipoprotein E ($\text{APOE}$) genotype was $\varepsilon3/\varepsilon4$.

**CASE 2**

A 54-year-old woman presented for evaluation owing to 1 year of progressive language impairment involving difficulties with word finding, remembering names, and ex-
pressing herself. Her family said her speech was occasionally nonsensical, describing it “like a word salad.” Within a few months, she developed difficulty writing and spelling, as well as decreased speech output. There were no reported problems with recognizing words. Memory complaints were minimal and, other than anxiety, there was no change in personality or behavior. She had some difficulty with navigation but did not get lost, and there were no motor symptoms.

Her examination was notable for long word-finding pauses and sparse speech, mostly consisting of single words and short phrases. There were no articulation problems. She could follow simple commands but had difficulty with complex instructions. She scored 14 of 30 on the Mini-Mental State Examination. On neuropsychologic testing, she displayed poor verbal memory (that benefited from recognition), impairment in working memory and executive functions, and language impairment including impairment in repetition, comprehension of syntactically complex sentences, confrontational naming (that benefitted from multiple choice), and verbal fluency (Table).

Voxel-based morphometry was performed on her 1.5-T magnetic resonance imaging (preprocessing and analysis, as in case 1) and was compared against 16 control subjects matched as previously described (Figure 1B). There was asymmetric atrophy involving the left temporal lobe, left medial and inferior frontal regions, and left inferior parietal lobe.

She had a family history of dementia, including a father who died mute at age 65 years and a paternal grandmother and brother who had been diagnosed as having FTD. Her genetic testing revealed a novel GRN mutation, affecting the first protein residue (g.1A>T, p.M1?). Other distinct pathogenic mutations of the same residue have been reported (g.1A>G, p.M1?; g.2T>C, p.M1?; and g.3G>A, p.M1?). Her APOE genotype was ε3/ε4.

The patient died at age 55 years, and an autopsy was performed 8 days post mortem. The entire brain showed advanced autolysis, which precluded meaningful observations about cerebral atrophy and limited immunohistochemical analysis. Nonetheless, immunohistochemistry for Aβ (3F4 antibody, hematoxylin counterstain) (A) and sparse to moderate neurofibrillary tangles and neuropil threads are seen (PHF-1 antibody, hematoxylin counterstain) (B). C. Dorsolateral frontal cortex shows frequent TAR DNA-binding protein 43 (TDP-43)—immunoreactive crescentic or compact neuronal cytoplasmic inclusions with surrounding wispy neuropil threads, consistent with frontotemporal lobar degeneration–TDP, type A. Scale bars indicated 500 µM (A), 100 µM (B), and 50 µM (C).

We present 2 patients with a clinical presentation consistent with AD, one an amnestic type and the other sug-
gestive of logopenic progressive aphasia, a syndrome typically caused by AD pathology. One patient had a positive amyloid PET scan demonstrating fibrillary amyloid pathology suggestive of AD and the other had autopsy confirmation of AD pathology. Notably, both patients harbored a GRN mutation, which predicts underlying FTLD-TDP pathology rather than AD.

Mutations in GRN have been associated with several clinical syndromes, including behavioral-variant FTD (bvFTD), nonfluent primary progressive aphasia, and corticobasal syndrome. Prior studies have also noted that 9% to 17% of GRN mutation carriers may present with an AD phenotype. While pathologic validation is lacking in most cases, one such patient had both AD and FTLD-TDP at autopsy and another showed an AD-like cerebrospinal fluid biomarker profile with an AD-like syndrome (low Aβ42 and elevated total tau). Other studies have indicated that polymorphisms in GRN modify the risk for developing AD. As prior clinicopathological series of GRN have shown only rare evidence of copathology with AD, if there is a risk for AD conferred by alterations in GRN, the association is less direct than with FTLD.

Prior data on the influence of APOE status on clinical phenotype in GRN carriers has been mixed, with one study showing early memory problems in ε4 allele carriers, and other studies showing no clear modulatory effect on clinical symptoms. Both patients in this report were heterozygous for the APOE ε4 allele. It is possible that AD pathology found in these patients was strictly due to APOE ε4 status, as the prevalence of amyloid deposition (as detected by Pittsburgh Compound B–PET imaging) is approximately 10% in 45-year-old to 59-year-old cognitively normal ε4 carriers, and 37% in 60-year-old to 69-year-old carriers. On the other hand, the early age at symptom onset and the AD-like clinical syndrome and atrophy pattern, as well as the advanced neurofibrillary pathology (Braak stage V), seen in case 2 argue that AD contributed to and perhaps was the main cause of dementia.

Mutations in GRN are thought to lead to neurodegeneration via haploinsufficiency, although the direct molecular link to TDP-43 translocation and aggregation remains unclear. Recent theories have focused on the anti-inflammatory properties of the progranulin protein. Mutations in GRN result in haploinsufficiency of functional progranulin, which might then result in a proinflammatory state. Patients with GRN mutations have been shown to have elevated levels of the proinflammatory cytokine interleukin 6. Functional progranulin promotes an increase in the anti-inflammatory cytokine interleukin 10 in macrophages, which would be decreased in haploinsufficiency. Progranulin interacts with tumor necrosis factor (TNF) receptors, thereby antagonizing TNF-α activity. Therefore, in a state of progranulin deficiency, relative TNF-α activity is increased.

This proinflammatory state might predispose not only to the development of FTLD, but to other forms of neurodegeneration. Alzheimer disease has also been linked to increased expression of inflammatory cytokines and microglial activation has been observed in AD post mortem and in vivo. Whether this activity is detrimental or protective and primary or secondary has been debated, but there is evidence suggesting that high levels of proinflammatory cytokines might decrease phagocytosis of Aβ by microglia. An increase in TNF-α is associated with cognitive decline in AD. In mouse models of AD, TNF-α is implicated in enhanced amyloid production, tau hyperphosphorylation, and cell death, and countering TNF-α improves both symptoms and pathology.

In AD, abnormal TDP-43 staining is seen in up to 34% of cases. In most cases of comorbid AD/FTD, TDP inclusions are restricted to the medial temporal lobe, but a minority of cases shows a more widespread deposition pattern consistent with FTLD-TDP type A, the same pattern associated with GRN cases. The molecular links between TDP-43 and AD pathologies are not known. One study found elevated TDP-43 levels in an AD mouse model that correlated with Aβ oligomers; decreasing Aβ42 levels normalized TDP-43 in these mice. Whether this relationship could be bidirectional and TDP-43 levels may contribute to Aβ deposition as well is a topic for further investigation.

The present cases add support to the association between GRN and AD. As pathology from more cases becomes available, the strength and frequency of this association will be clarified.

Accepted for Publication: August 17, 2012.
Published Online: April 22, 2013. doi:10.1001/2013.jama-neuro.393

Correspondence: David C. Perry, MD, University of California, San Francisco (UCSF) Memory and Aging Center, MC: 1207, 675 Nelson Rising Lane, Suite 190, San Francisco, CA 94158 (dperry@memory.ucsf.edu).


Conflict of Interest Disclosures: Dr Perry’s work is funded by grant T32 AG23481 from the National Institutes of Health’s National Institute on Aging, Dr Lehmans work is funded by Alzheimer’s Research UK. Dr Yokoyama’s work is funded by a diversity supplement through grant P50 AG03006 from the National Institutes of Health’s National Institute on Aging, Dr Lehmans work is funded by Alzheimer’s Research UK. Dr. Coppola’s work is funded by R01 AG026938 and RCI AG035610 from the National Institutes of Health’s National Institute on Aging. Dr. Grinberg’s work is supported by the John Douglas French Alzheimer’s Foundation and grants P50 AG023501-06 and 1R1AG040311-01 from the National Institutes of Health. Dr. Rosen’s work is supported by R01AG032306 and
REFERENCES


5. Le Ber I, Camuzat A, Hannequin D, et al; French Research Network on FTD/FTD-ALS. Mutations in progranulin are a major cause of ubiquitin-positive frontotemporal dementia linked to chromosome 17q21. 2006;442(7105):916-919.


©2013 American Medical Association. All rights reserved.