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Progranulin mutations as a risk factor for Alzheimer's Disease

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Abstract

Objective—To describe patients with progranulin gene (*GRN*) mutations and evidence of Alzheimer's disease (AD) pathology

Design—Two case reports and literature review

Setting—University of California San Francisco Memory and Aging Center

Patients—Two unrelated patients with *GRN* mutations

Results—One patient presented at age 65 with a clinical syndrome suggestive of AD and showed evidence of amyloid aggregation on positron emission tomography. Another patient presented at age 54 with logopenic progressive aphasia and at autopsy showed both frontotemporal lobar degeneration with TDP-43 inclusions and AD.

Conclusions—In addition to autosomal-dominant frontotemporal lobar degeneration, mutations in *GRN* may be a risk factor for AD clinical phenotypes and neuropathology.

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Introduction

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's disease (AD), it is thought these various presentations all result from TDP-43 pathology. Here we present two patients who suggest *GRN* mutations may also be a risk factor for AD pathology.

Report of Case #1

A 65 year-old right-handed man presented with three 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 agraphesthesia. He scored 17/30 on the Mini-Mental State Examination (MMSE)[1]. Detailed neuropsychological testing revealed poor verbal and visual memory, confrontational naming, and executive function with relative preservation of visuospatial skills (Table).

Voxel-based morphometry (VBM)[2] was performed on the patient's 3 T magnetic resonance imaging (MRI) scan using SPM8 (http://www.fil.ion.ucl.ac.uk/spm/). Pre-processing included segmentation into gray and white matter, alignment and warping with DARTEL [3], normalization to Montreal Neurological Institute (MNI) space, modulation and smoothing with an 8 mm full width at half maximum (FWHM) Gaussian kernel. Single-subject VBM 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, neuropsychological testing, and imaging he was diagnosed with AD.

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

The patient had a family history of FTD in three maternal relatives. His father had late-life dementia and paternal grandmother was diagnosed with AD. Genetic testing revealed that the patient carried a the same novel mutation in *GRN* as his affected maternal family members, an octanucleotide insertion in the coding region (c.1263_1264insGAAGCGAG)

causing frameshift and premature translation termination, predicted to result in nonsense-mediated mRNA decay. Apolipoprotein E (*APOE*) genotype was E3/E4.

Report of Case #2

A 54 year-old woman presented for evaluation due to one year of progressive language impairment involving difficulties with word finding, remembering names, and expressing herself. Her family described her speech as occasionally nonsensical “like a word salad.” Within a few months she developed difficulty writing, spelling, and 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 14/30 on the MMSE and on neuropsychological testing she displayed poor verbal memory (that benefitted 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).

VBM was performed on her 1.5 T MRI (pre-processing and analysis as in Case 1) and was compared against 16 controls matched as described above (see 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 65, and a paternal grandmother and brother with a diagnosis of 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?, PMID: 18245784, g. 2T>C, p.M1?, PMID: 16862116, 16950801, and g.3G>A, p.M1?, PMID: 16862115). Her *APOE* genotype was E3/E4.

The patient died at age 55, and an autopsy was performed eight days post-mortem. The entire brain showed advanced autolysis, which precluded meaningful observations about cerebral atrophy and limited immunohistochemical analysis. Nonetheless, immunohistochemistry for beta-amyloid (3FR antibody, anti-mouse, 1:250, Millipore, Billerica, MA, USA), hyperphosphorylated tau (PHF-1 antibody, anti-mouse, 1:250, courtesy Peter Davies), and TDP-43 (anti-rabbit, 1:2000, Proteintech Group, Chicago, IL, USA) was performed on a subset of regions showing relative tissue integrity, including medial temporal lobe, middle frontal gyrus, pre- and post-central gyri, angular gyrus, superior temporal gyrus, and lateral occipital cortex. These analyses revealed moderate to frequent neuritic amyloid plaques (Figure 3A) in all regions examined and moderate to frequent tau-positive neurofibrillary tangles in medial temporal and neocortical regions (Figure 3B) but not primary sensorimotor cortex, consistent with NIA-Reagan criteria for high likelihood AD[4] and a Braak AD stage of V.[5] In addition, we observed superficial greater than deep laminar TDP-43 pathology consisting of moderate to frequent small round or crescentic neuronal cytoplasmic inclusions and neuropil threads (Figure 3C) accompanied by scarce neuronal nuclear inclusions and glial cytoplasmic inclusions (not pictured), consistent with FTLD-TDP, harmonized Type A,[6] the subtype seen in *GRN* mutation carriers.

Comment

We present two patients with a clinical presentation consistent with AD, one an amnestic type, and the other suggestive of logopenic progressive aphasia, a syndrome typically caused by AD pathology.[7] 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.

GRN mutations have been associated with several clinical syndromes including behavioral variant frontotemporal dementia (bvFTD), nonfluent primary progressive aphasia, and corticobasal syndrome.[8] Prior studies have also noted that 9–17% of *GRN* mutations carriers may present with an AD phenotype.[8,9] While pathologic validation is lacking in most cases, one such patient had both AD and FTLD-TDP at autopsy,[10] and another showed an AD-like CSF biomarker profile with an AD-like syndrome (low $A\beta_{42}$ and elevated total tau).[11] Other studies have indicated that polymorphisms in *GRN* modify the risk of developing AD.[12–14] As prior clinicopathological series of *GRN* have shown only rare evidence of co-pathology with AD,[9,10] if there is a risk of 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 E4 allele carriers,[9] and two other studies showing no clear modulatory effect on clinical symptoms.[15,16] Both patients in this report were heterozygous for the *APOE4* allele. It is possible that AD pathology found in these patients was strictly due to *APOE4* status, as the prevalence of amyloid deposition (as detected by PiB-PET) is ~10% in 45–59 year-old cognitively normal E4-carriers, and 37% in 60–69 year-old carriers.[17] On the other hand, the early age of 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.

GRN mutations are thought to lead to neurodegeneration via haploinsufficiency, though 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.[18] *GRN* mutations result in haploinsufficiency of functional progranulin, which might then result in a pro-inflammatory state. Patients with *GRN* mutations have been shown to have elevated levels of the pro-inflammatory cytokine interleukin-6 (IL-6).[19] Functional progranulin promotes an increase in the anti-inflammatory cytokine IL-10 in macrophages[20] which would be decreased in haploinsufficiency. Progranulin interacts with tumor necrosis factor (TNF) receptors, thereby antagonizing TNFα activity.[21] In a state of progranulin deficiency relative TNFα activity is therefore increased.

This pro-inflammatory state might predispose not only to development of FTLD, but to other forms of neurodegeneration. AD has also been linked to increased expression of inflammatory cytokines,[22] and microglial activation has been observed in AD post-mortem[23] and *in-vivo*.[24] Whether this activity is detrimental or protective and primary or secondary has been debated, but there is evidence suggesting that high levels of pro-inflammatory cytokines might decrease phagocytosis of beta amyloid by microglia.[25] An increase in TNFα is associated with cognitive decline in AD.[26] In mouse models of AD, TNFα is implicated in enhanced amyloid production,[27] tau hyperphosphorylation and cell death,[28] and countering TNFα improves both symptoms and pathology.[29,30] Beta amyloid aggregation in mouse hippocampus and cortex has also been induced by inflammation.[31]

In AD, abnormal TDP-43 staining is seen in up to 34% of cases.[32] In most cases of comorbid AD/TDP, 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.[33] 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.[34] 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 the frequency of this association will be clarified.

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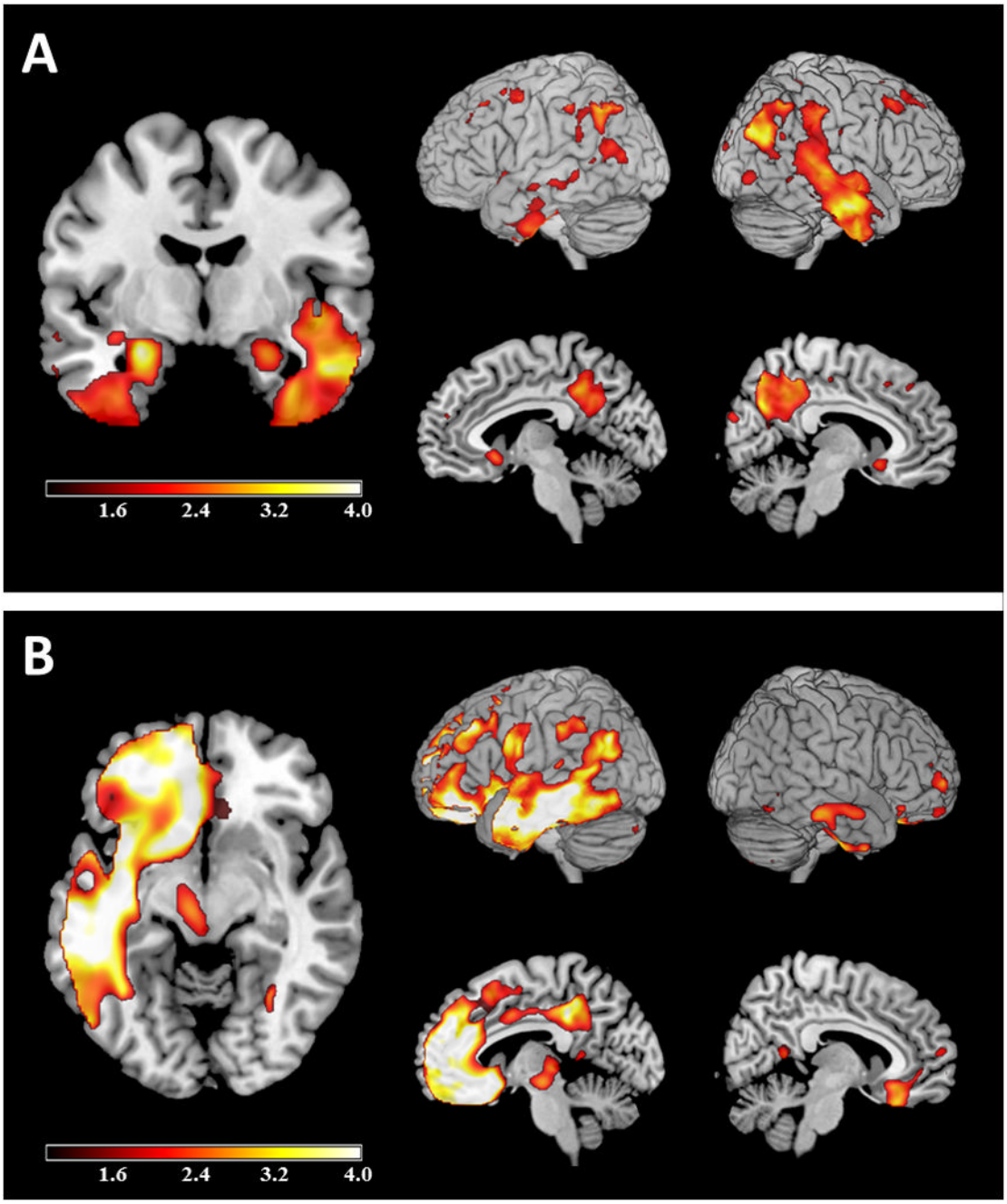

Figure 1.
Voxel-based morphometry. Single subject voxel-based morphometry of Case 1 (A) and Case 2 (B), uncorrected for multiple comparisons at $p<0.05$, displayed as T map ($1<T<4$) and overlaid on MNI template brain. Images are displayed in neurological convention.

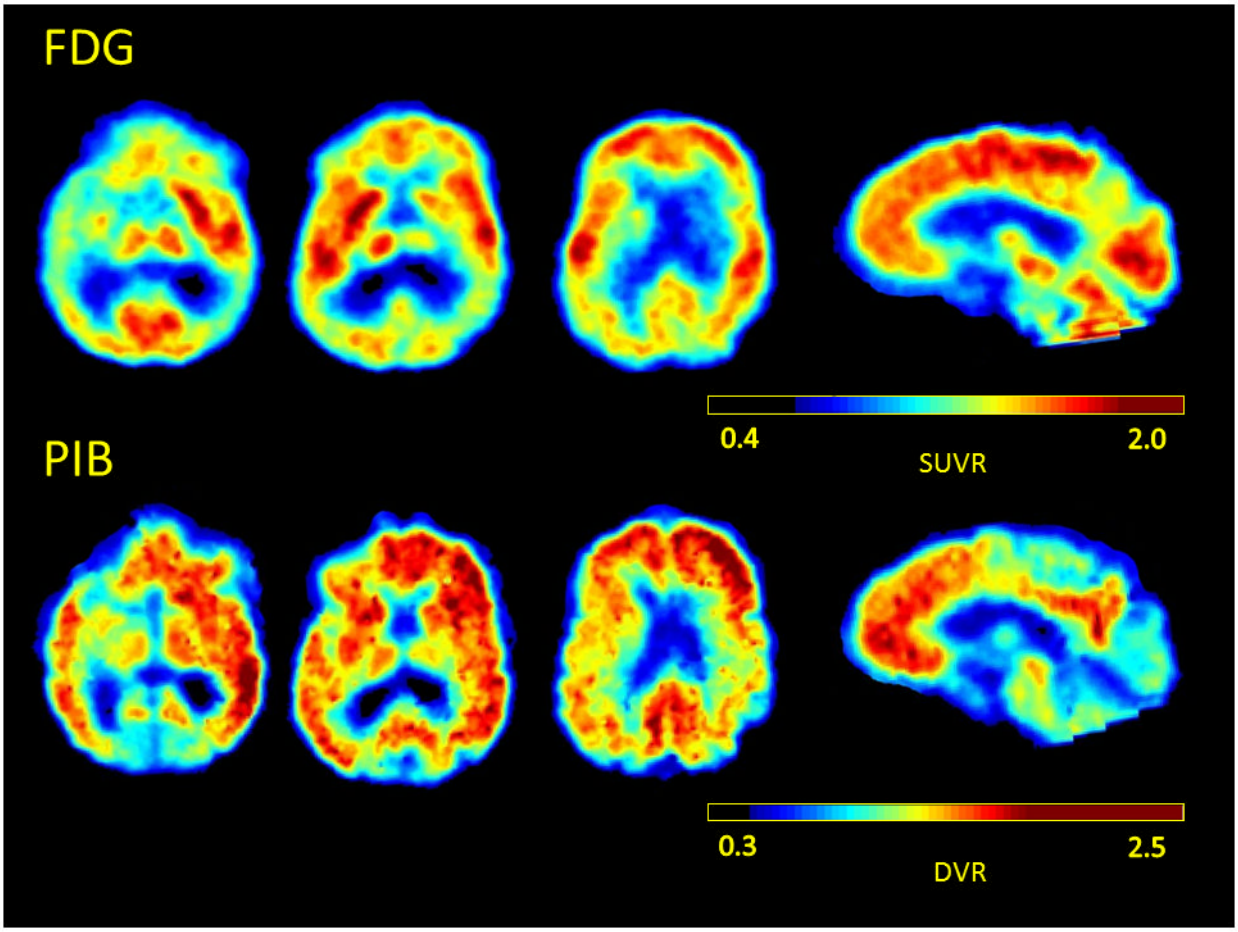

Figure 2.
PET imaging of case 1. *(top)* FDG-PET showing bilateral temporoparietal hypometabolism and *(bottom)* Pittsburgh compound B (PiB-PET) image of Case 1 showing amyloid tracer binding.

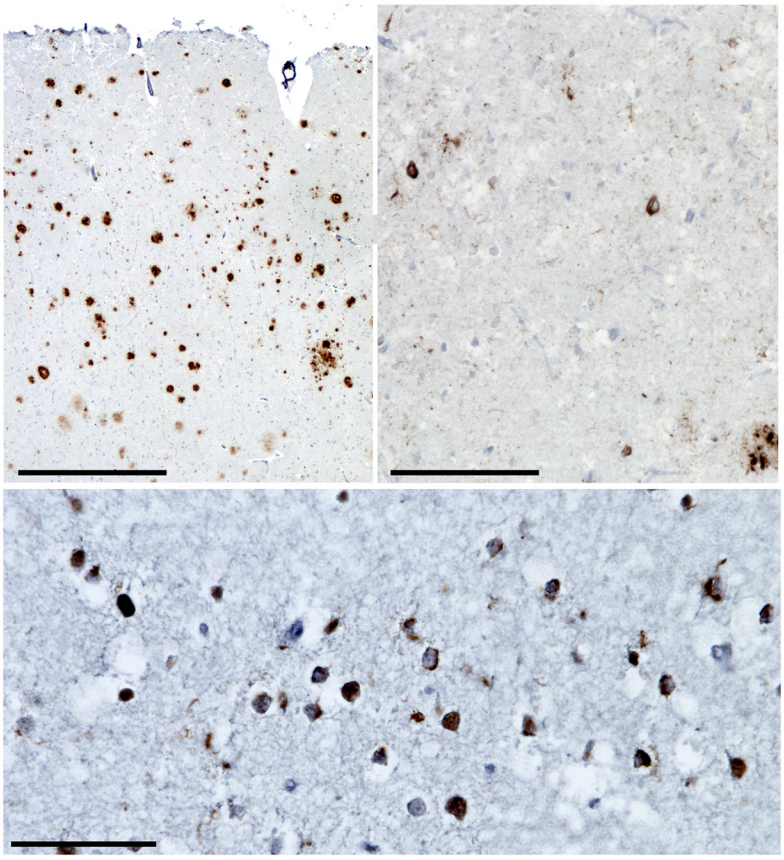

Figure 3.
Pathological findings for case 2. In the angular gyrus, (A) frequent amyloid-beta positive neuritic plaques (3F4 antibody, hematoxylin counterstain) and (B) sparse to moderate neurofibrillary tangles and neuropil threads are seen (PHF-1 antibody, hematoxylin counterstain). (C) Dorsolateral frontal cortex shows frequent TDP-43-immunoreactive crescentic or compact neuronal cytoplasmic inclusions with surrounding wispy neuropil threads, consistent with FTLD-TDP, Type A. Scale bars indicated 500 μM (A), 100 μM (B), and 50 μM (C).

Table

Neuropsychological Testing

		Normal values by age and education for case 1* (SD)	Case 1 (age 65)	Normal values by age and education for case 2* (SD)	Case 2 (age 54)
General	MMSE (max 30)	-----	17	-----	14
Memory	CVLT short form delayed recall (max 9)	7.8 (1.4)	0	7.9 (1.5)	0
	Recognition (max 9)	8.7 (0.5)	3	8.8 (0.4)	6
	Recall false positives	0.6	12	-----	3
	Benson figure delayed recall (max 17)	11.5 (2.8)	0	12.6 (2.3)	12
Visuospatial	Benson figure copy (max 17)	15.5 (1.1)	16	15.5 (1.1)	15
Language	Modified BNT (max 15)	14.3 (0.8)	11	14.5 (0.9)	2
	BNT Multiple choice	-----	2	-----	11
	Repetition (max 5)	4.6 (0.6)	1	4.7 (0.7)	1
	Sentence comprehension (max 5)	-----	5	-----	1
	PPVT-R (max 16)	15.6 (0.8)	15	15.7 (0.8)	6
Executive	Digit span backwards	5.8 (1.2)	3	5.4 (1.3)	2
	Phonemic fluency (D word generation)	16.3 (4.5)	13	15.0 (3.9)	1
	Semantic fluency (animal generation)	23.5 (5.0)	12	22.7 (4.7)	3

*Age-adjusted normal values derived from University of California San Francisco Memory and Aging Center cohort

MMSE=Mini-Mental State Examination, CVLT=California Verbal Learning Test, BNT=Boston Naming Test, PPVT=Peabody Picture Vocabulary Test

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