Neuropathologic Heterogeneity in HDDD1: A Familial Frontotemporal Lobar Degeneration With Ubiquitin-positive Inclusions and *Progranulin* Mutation

Maria I. Behrens, MD, PhD,† Odity Mukherjee, PhD,*‡ Pang-hsien Tu, MD, PhD,*§ Rajka M. Liscic, MD, PhD,*‖ Lea Tenenholz Grinberg, MD,*§¶ Deborah Carter, HT,*§ Katherine Paulsmeyer, BS,*§ Lisa Taylor-Reinwald, BA,*§ Michael Gitcho, PhD,*# Joanne B. Norton, MSN, CS,*‡ Sumi Chakraverty, MS,*‡ Alison M. Goate, DPhil,*‡ John C. Morris, MD,*§# and Nigel J. Cairns, PhD, MRCPath*§*

Abstract: Hereditary dysphasic disinhibition dementia (HDDD) describes a familial disorder characterized by personality changes, and language and memory deficits. The neuropathology includes frontotemporal lobar atrophy, neuronal loss and gliosis and, in most cases, abundant Aβ plaques and neurofibrillary tangles (NFTs). A Pick/Alzheimer's spectrum was proposed for the original family (HDDD1). Here we report the clinicopathologic case of an HDDD1 individual using modern immunohistochemical methods, contemporary neuropathologic diagnostic criteria to distinguish different frontotemporal lobar degenerations (FTLDs), and *progranulin* (*PRGN*) mutation analysis. Clinical onset was at age 62 years with personality changes and disinhibition, followed by nonfluent dysphasia, and memory loss that progressed to muteness and total dependence with death at age 84 years. There was severe generalized brain atrophy (weight = 570 g). Histopathology showed superficial microvacuolation, marked neuronal loss, gliosis, and ubiquitin-positive, tau-negative cytoplasmic and intranuclear neuronal inclusions in frontal, temporal, and parietal cortices. There were also frequent neuritic plaques and NFTs in parietal and occipital cortices. The case met neuropathologic criteria for both FTLD with ubiquitin-positive, tau-negative inclusions (FTLD-U), and Alzheimer disease (Braak NFT stage V). We discovered a novel pathogenic *PGRN* mutation c.5913 A > G (IVS6-2 A > G) segregating with FTLD-U in this kindred. In conclusion, HDDD1 is an FTLD-U caused by a *PGRN* mutation and is neuropathologically heterogeneous with Alzheimer disease as a common comorbidity.

Key Words: frontotemporal lobar degeneration, FTLD-U, HDDD1, progranulin mutation, Alzheimer disease

(*Alzheimer Dis Assoc Disord* 2007;21:1–7)

The term hereditary dysphasic dementia was used in 1984 by Morris et al[1] to describe a kindred of Central-European origin with an autosomal dominant disorder that was characterized by insidious onset in adulthood of changes in behavior and personality, language abnormalities, and memory loss. It was later renamed hereditary dysphasic disinhibition dementia type 1 (HDDD1), to both highlight the behavioral features and recognize another kindred (HDDD2) with a similar phenotype.[2] The mean age at symptom onset for HDDD1 is 62 years. The primary symptoms are dysphasia (primarily word hesitancy, diminished phrase length, reduction in spontaneous speech, and dysnomia), disinhibition, and bulimia. In addition, dementia (characterized by memory deficits and spatial disorientation), parkinsonism, and focal neurologic signs (hemiparesis and extensor plantar signs) characterize most cases. The disease progresses to muteness, prostration, and severe dementia with an average survival of approximately 8 years.

At autopsy, HDDD1 was marked by left greater than right cerebral atrophy, principally in the frontal and anterior temporal lobes, with corresponding ventricular dilatation (Fig. 1). Histopathologic features included conspicuous spongiform degeneration of the superficial cortical layers (microvacuolation), which in some regions extended across all cortical laminae, pronounced neuronal loss and dense gliosis, both cortical and subcortical (Fig. 2A). No Pick bodies or ballooned cells were present. In addition, in 3 out of 4 cases, there were abundant Aβ plaques in the frontal cortex and neurofibrillary tangles

Received for publication May 10, 2006; accepted November 2, 2006.

From the *Alzheimer's Disease Research Center; Departments of §Pathology and Immunology; ‡Psychiatry; #Neurology, Washington University School of Medicine, St Louis, MO; †Departamento de Neurología y Neurocirugía, Hospital Clínico Universidad de Chile and Clínica Alemana, Santiago, Chile; ‖Institute for Medical Research and Occupational Health, Zagreb, Croatia; and ¶Department of Pathology, University of Sao Paulo Medical School, Sao Paulo, Brazil.

Support by grants from the National Institute on Aging of the National Institutes of Health (P01 AG-03991 and P50 AG-05681). Odity Mukherjee is a Fogarty International Postdoctoral fellow (Grant No. TW 0511-05). Rajka M. Liscic was supported by a J. William Fulbright Foreign Scholarship (Grant No. 68428174).

Reprints: Nigel J. Cairns, PhD, MRCPath, Department of Pathology and Immunology, Washington University School of Medicine, Campus Box 8118, 660 South Euclid Avenue, St Louis, Missouri 63110 (e-mail: cairns@wustl.edu).

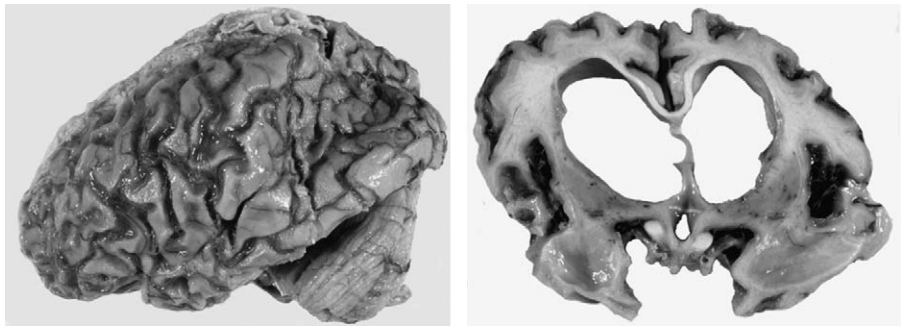

FIGURE 1. Macroscopy of HDDD1 with FTLD-U and *PGRN* mutation. On the left, global atrophy of the left hemibrain of case no. 1. Gyri are markedly shrunken and sulci widened. The cerebellum is relatively well-preserved. On the right, a coronal slice of the prefrontal lobe showing marked cortical atrophy and ventricular dilatation.

(NFTs) in the hippocampus. The disorder was considered part of a Pick-Alzheimer spectrum of cortical neuronal degeneration.

An additional member of the HDDD1 kindred recently came to autopsy, providing us with the opportunity to reexamine the original concept of a Pick-Alzheimer spectrum with the application of modern immunohistochemical methods and current criteria for dementing disorders, including frontotemporal lobar degeneration (FTLD),[3–5] and genotyping for mutations in amyloid precursor protein (*APP*), presenilin 1 and 2 (*PS1* and *PS2*), microtubule-associated protein tau (*MAPT*), and the recently identified gene, progranulin (*PGRN*), which has been shown to cause familial FTLD-U, including HDDD2.[6,7]

METHODS

Subjects

Clinical information for the case was obtained by interviews with family members, review of medical records, and a detailed neurologic examination at age 74 by one of the authors (J.C.M.). To determine the variability in pathology in members of the HDDD1 family the current case was compared with archival tissues from 3 of the original cases (IV-1, IV-2, and IV-6).[1] Tissue blocks from the fourth case, IV-7, after an extensive search were unavailable for this study.

Neuropathology

The brain was fixed in formalin, paraffin wax-embedded, and sections cut at 6 μm. Blocks were taken from: frontal, temporal, parietal, and occipital lobes, thalamus, striatum including the nucleus basalis of Meynert, amygdala, hippocampus, midbrain, pons, medulla oblongata, and the cervical spinal cord. Tissue blocks were available from 3 of 4 of the original cases and contemporary immunohistochemistry was performed on these 3 cases, where blocks or unstained sections were available, and compared with the recent case. Histologic stains included: hematoxylin and eosin, Luxol fast blue-hematoxylin with periodic acid-Schiff; cresyl echt violet; modified and Hedreen-Bielschowsky and Gallyas silver impregnations. Immunohistochemistry was performed using the following antibodies: β-amyloid (Aβ) (10D5, Elan Pharmaceuticals, San Francisco, CA, and AG8, Senetek, St Louis, MO); phosphorylated tau, (PHF-1 and Alz-50, kindly supplied by Dr Peter Davies, Albert Einstein Medical School, Bronx, NY; and AT8, Innogenetics, Belgium), glial fibrillary acidic protein (GFAP, Dako, Denmark); ubiquitin (Dako, Denmark and East Acres, MA), α-synuclein (LB-509, Zymed, CA), and progranulin (R&D Systems, CA). To distinguish between tau-positive, ubiquitin-positive and tau-negative, ubiquitin-positive inclusions, double PHF-1 and ubiquitin immunohistochemistry was performed.

DNA Sequencing

High molecular weight DNA was extracted from brain and/or peripheral blood tissue. DNA was available from 4 individuals (one affected with autopsy confirmation). Sequence analysis was performed on all coding exons and flanking intronic sequences of *APP*, *PS*, *MAPT*, and *PGRN* genes. Direct sequencing of the amplified fragments was performed using Big Dye Terminator Cycle Sequencing Ready Reaction Kit (Applied Biosystems, Wellesley, MA) on an ABI 3100 sequencer using standard protocols. Mutation detection was performed using the program Sequencher V4.6 (Gene Codes Corporation, Ann Arbor, MI). Sequence variants were confirmed by comparing genotype status with 45 unrelated clinically confirmed control individuals and subsequently tested for segregation with the disease in the kindred.

RESULTS

Clinical Features

The patient represents family member IV-4 of a 7-generation family of German heritage.[1] At age 62 years there was a change in personality, with egocentricity, irritability, and abuse of alcohol. Three years later she developed nonfluent dysphasia with difficulty naming objects and mild memory loss. At age 66 years she became sexually aggressive and wandered about the neighborhood at night. There was reduced spontaneous output and perseveration of speech with paraphasic errors. She was placed in a nursing home at age 69 years because of difficulties in management. A medical report 2 years later recorded restlessness, impaired auditory comprehension with nonfluent speech, and literal paraphasias. She was unable to read or write. She knew right from left and was

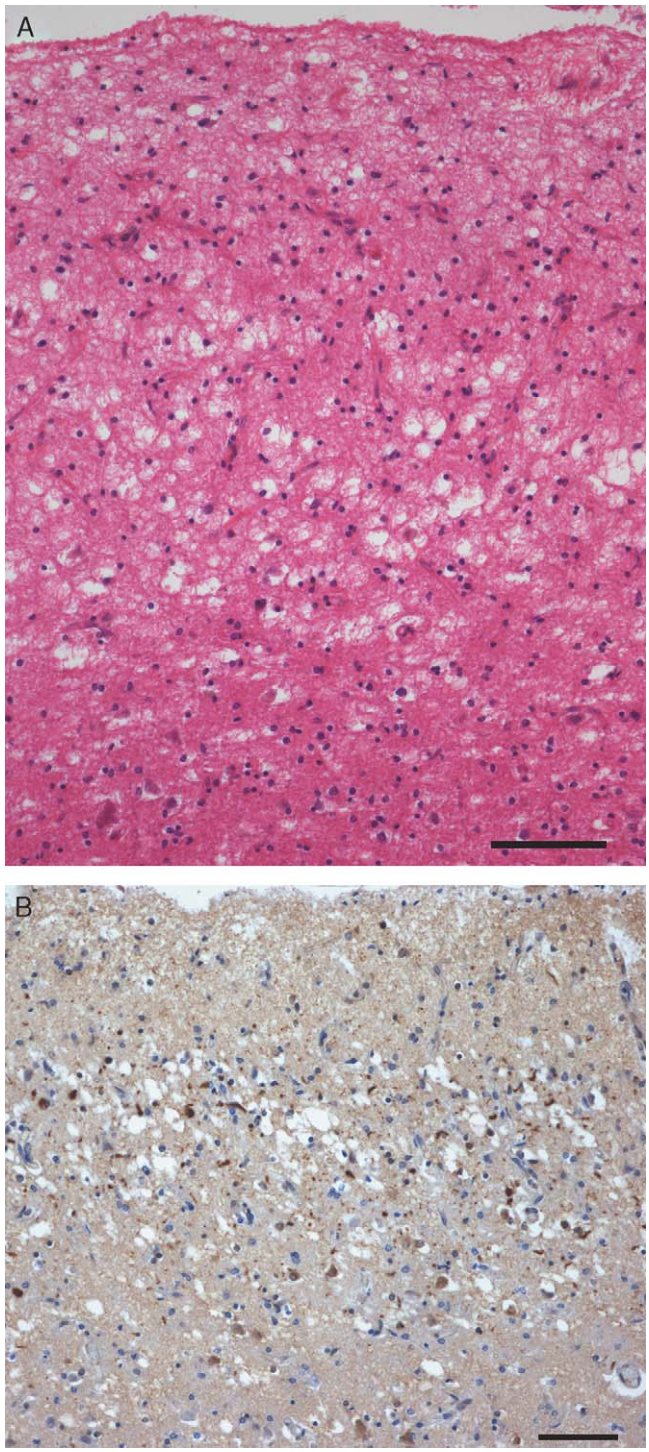

FIGURE 2. Microscopy of HDDD1 with FTLD-U and *PGRN* mutation. A, Transcortical neuronal loss, microvacuolation, and gliosis in the frontal neocortex of case no. 3. Hematoxylin and eosin. B, Low power micrograph of ubiquitin-positive, tau-negative inclusions in the superficial cortical layers of the temporal neocortex of case no. 3. Ubiquitin immunohistochemistry. Bars = 100 μm.

able to copy simple, 2-dimensional figures. There were no physical or focal neurologic abnormalities. By age 72 years the patient was virtually mute, unable to walk or eat without assistance, and did not recognize family members. The examination at 74 years of age showed flexion contractures in both hips and knees and no spontaneous movements except to follow the examiner with the eyes. There was mild right hemiparesis of the face, arm, and leg with bilateral extensor plantar responses. Right greater than left resting tremor was present, with cogwheel rigidity in both wrists and elbows. Positive snout and suck reflexes, and bilateral grasp reflexes were elicited. She remained in a vegetative state for nearly 12 years and died of aspiration pneumonia at age 84 years.

Neuropathology

The brain was severely and globally atrophic, weighing 570 g at the time of autopsy (Fig. 1). The substantia nigra and locus coeruleus were depigmented. Histologic sections disclosed varying degrees of neuronal loss and gliosis affecting many regions (Table 1). There was a disparity between the microscopic appearance of the frontal and temporal lobes and the parietal and occipital lobes. The characteristic features of FTLD were present: FTLD, neuronal loss, microvacuolation that was sometimes confluent in upper cortical laminae, and astrocytic gliosis. Although neuronal loss and astrocytosis involved the entire cortex in some areas, scattered ubiquitin-positive, tau-negative neuronal cytoplasmic inclusions (NCIs), dystrophic neurites (DNs), and occasional neuronal intranuclear inclusions (NIIs) were seen predominantly in the frontal and temporal lobes (Fig. 2), and to a lesser degree in the parietal lobe and subcortical nuclei (Table 2) (Fig. 3). These lesions are identical to those seen in other members of this family (cases 2 to 4), and in both familial cases of FTLD-U with *PRGN* mutations[6,7] and in some sporadic cases. In this brain there was additional Alzheimer disease (AD) pathology in the parietal and occipital lobes and to a lesser degree the temporal lobe (Figs. 4, 5). Scattered NFTs, neuropil threads, and neuritic plaques (NPs) were present throughout the affected cortices with the highest densities in the parietal and medial occipital lobes. The NFT pathology was consistent with Braak NFT stage V and amyloid stage C. In contrast to the relative abundance of AD pathology in the parietal and occipital lobes, Aβ plaques and NFTs were relatively sparse in the frontal and temporal lobes. No Pick bodies were present. Neurofibrillary tangles were observed in the CA4-CA2 subfields of the hippocampus and dentate gyrus, and the CA1 subfield and subiculum had severe loss of neurons with astrocytic gliosis. The nucleus basalis of Meynert was unremarkable, similar to the original case series which had no or minimal changes.[1] There was loss of neurons from the substantia nigra and tau-immunoreactive NFTs and pretangles were present in the pigmented nuclei. Scattered diffuse Aβ deposits were present in the cerebellum. PGRN immunohistochemistry revealed that

TABLE 1. Distribution and Severity of Neuronal Loss and Gliosis in HDDD1 With *PGRN* Mutation

	Neuronal Loss and Gliosis			
Brain Area	**Case No. 1 IV-4***	**Case No. 2 IV-6***	**Case No. 3 IV-2***	**Case No. 4 IV-1***
Brain weight, fixed (g)	570	NA	810	NA
Frontal lobe	+ + +	+ + +	+ + +	+ + +
Temporal lobe	+ + +	+ + +	+ + +	+ + +
Parietal lobe	+ +	+	+ + +	+ + +
Occipital lobe	+ +	NA	+ + +	+
Amygdala	+ + +	+	NA	+
Entorhinal cortex	+ + +	+	+ + +	+
Hippocampus				
CA1	+ + +	+	+ +	+ +
CA2-CA4	+ +	0	+	+
Dentate fascia	+ +	+	+	+
Caudate nucleus	+ + +	+	+	+
Putamen	+ +	+	+	+
Nucleus basalis of Meynert	0	+	NA	+
Thalamus	+	+	+	+
Substantia nigra	+ +	+ +	NA	+ +
Locus coeruleus	+	0	NA	+
Inferior olivary nucleus	+	0	NA	0
Cerebellum	+	0	+	+

*Patient No. as in Ref. 1.
NA indicates not available. Density of lesions: 0, none; +, few/mild; + +, moderate; + + +, severe/many.

this protein was not present in the ubiquitin-positive, tau-negative inclusions.

Direct DNA Sequencing Analysis

Sequence analysis of the *PGRN* gene identified a novel heterozygous mutation at the 5′ splice site of exon 7 (IVS6-2A > G). The mutation was found to cosegregate with FTLD-U and at risk individuals but was absent in the unaffected members (Fig. 6). Mutation c.5913 A > G (IVS6-2A > G) is predicted to cause the splicing out of exon 7 thereby resulting in an aberrant transcript.[8] Analysis of the 14 *tau* exons and the 480 base pairs of the *tau* promoter failed to show mutations in the sample examined. Similarly, there were no mutations in the *APP*, *PS1*, and *PS2* genes. The patient (case no. 1) carried *apolipoprotein E* alleles ε3 and ε4.

DISCUSSION

The present report describes clinical, pathologic, and genetic characteristics of a new member of the HDDD1 kindred with the application of modern immunohistochemical procedures and screening for *PGRN* mutations. The clinical presentation of this patient with a history of behavioral alterations, expressive language abnormalities, and deterioration of memory was very similar to the clinical presentation of other members of this family.[1] Clinically, the presentation of this and the other cases of the HDDD1 family can be

TABLE 2. Spectrum of Ubiquitin-positive, Tau-negative Inclusions and AD-Type Changes in HDDD1 With *PGRN* Mutation

		Case No.			
Brain Area	**Ubiquitinated Neuronal Inclusion**	**1**	**2**	**3**	**4**
Frontal neocortex	NCI	+ +	+ + +	+ +	+ +
	DN	+ +	+ +	+ +	+ +
	NII	+	+	+	+
Temporal neocortex	NCI	+ +	+ + +	+ +	+ +
	DN	+ +	+ +	+ +	+ + +
	NII	0	0	+	0
Dentate gyrus	NCI	+	+	+	+
	DN	0	0	0	0
	NII	+	0	+	0
Striatum	NCI	+ +	NA	NA	NA
	DN	+ +	NA	NA	NA
	NII	+	NA	NA	NA
Alzheimer-type changes					
Braak stage		V-C	II-C	II-C	I-B

NA indicates not available. Density of lesions: 0, none; +, few; + +, moderate; + + +, frequent. Alzheimer-type changes: Braak neurofibrillary tangle stage, range 0 to VI and amyloid stage, range 0 to C.

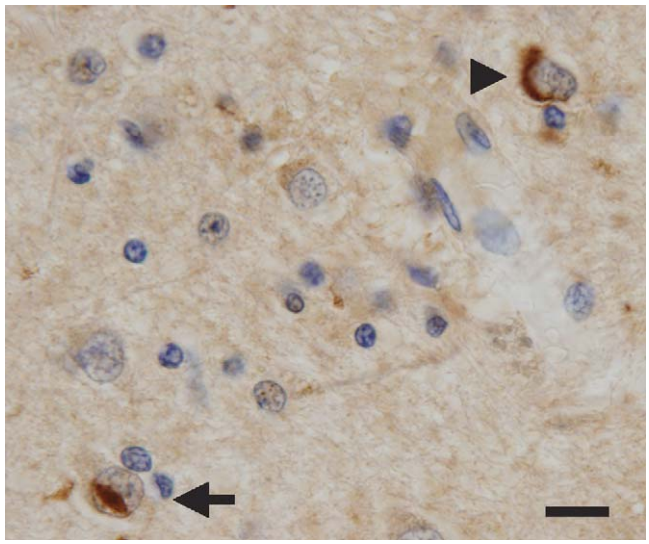

FIGURE 3. High power micrograph of ubiquitin-positive, tau-negative inclusions in the middle frontal gyrus of case no. 3 showing a NCI (arrowhead) and a NII (arrow). Ubiquitin immunohistochemistry. Bar = 50 μm.

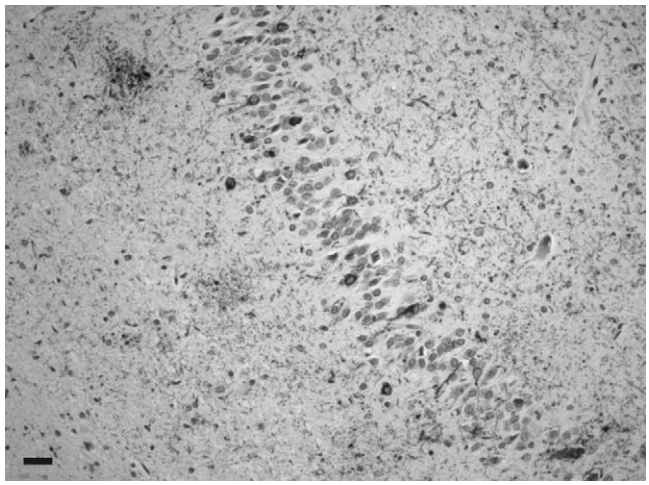

FIGURE 5. Phosphorylated tau inclusions in the dentate gyrus of the hippocampus of HDDD1 (case no. 1). DNs are present in the hippocampal subfield CA4 (right) and molecular layer (left). Tau (PHF1) immunohistochemistry. Bar = 10 μm.

classified as FTLD, frontotemporal dementia variant, according to current clinical diagnostic criteria.[4] The patient had an uncommonly protracted course of the disease after reaching the point of total care (total disease duration was 22 y).

The neuropathologic diagnosis of this new member of the HDDD1 pedigree met current accepted neuropathologic criteria for both FTLD-U (FTLD-motor neuron disease-type)[5] and AD according to the Consortium to Establish a Registry for Alzheimer's Disease (CERAD), and the National Institute on Aging (NIA)-Reagan Institute.[9] In the staging scheme of Braak, the NFT stage was V and amyloid stage C.[10] A similar pattern of a combination of frontotemporal neuronal loss, microvacuolation, gliosis, ubiquitin-positive inclusions, and features of AD pathology were present in 3 out of the 4 original cases in the HDDD1 kindred.[1] In the original report, Morris et al[1] proposed that the pathology of the disorder in this family belonged to an "Alzheimer-Pick spectrum." This designation was based primarily on the atrophy pattern because neither Pick cells, nor Pick bodies were present. Since the time of the original report, the clinicopathologic features are now characterized as FTLD-U, as the diagnosis of PiD is reserved for cases with tau-positive Pick bodies. According to current nosology,[5,11] the pathology of HDDD1 cases represents combined FTLD-U and AD. The symptomatic onset of the disorder was marked by the clinical features of FTLD. Combined with the pronounced devastation of the frontal lobes and relative sparing of the medial temporal lobes, the clinical onset suggests that FTLD-U is the primary disease followed by AD which affected those regions not already devastated by FTLD-U. As the devastation is so dramatic in this case, the possibility that these 2 distinct neurodegenerative disease processes act synergistically cannot be excluded.

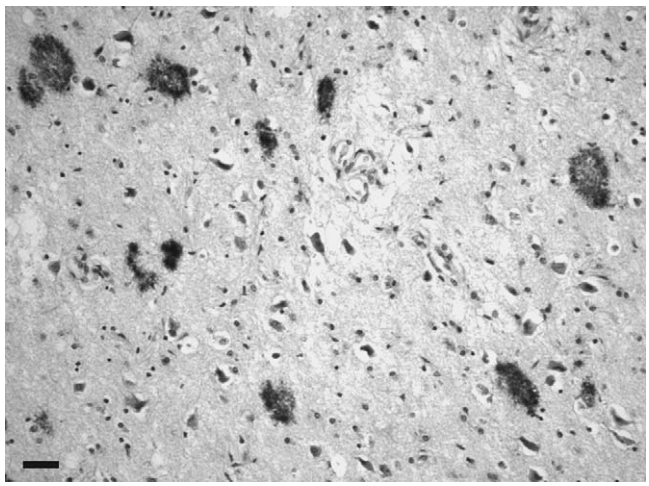

FIGURE 4. Aβ deposits in the temporal lobe of HDDD1 (case no. 1). Diffuse and more compact Aβ plaques are present. Aβ (10D5) immunohistochemistry. Bar = 10 μm.

A new finding not described in the original report of HDDD1[1] is the similarity between FTLD-U in this case and other familial cases of FTLD-U that have ubiquitin-positive, but tau- and Gallyas-negative inclusions in dentate fascia neurons and neocortex.[10–15] Although sporadic and familial amyotrophic lateral sclerosis cases show motor neuron loss and ubiquitin-positive, skeinlike inclusions in cranial motor nuclei including anterior horn cells of the spinal cord, these were absent in this case; the patient had no clinical signs of amyotrophic lateral sclerosis. The nucleus basalis of Meynert was preserved in the present case, a finding which was also observed with only minor neuronal loss in the original series of

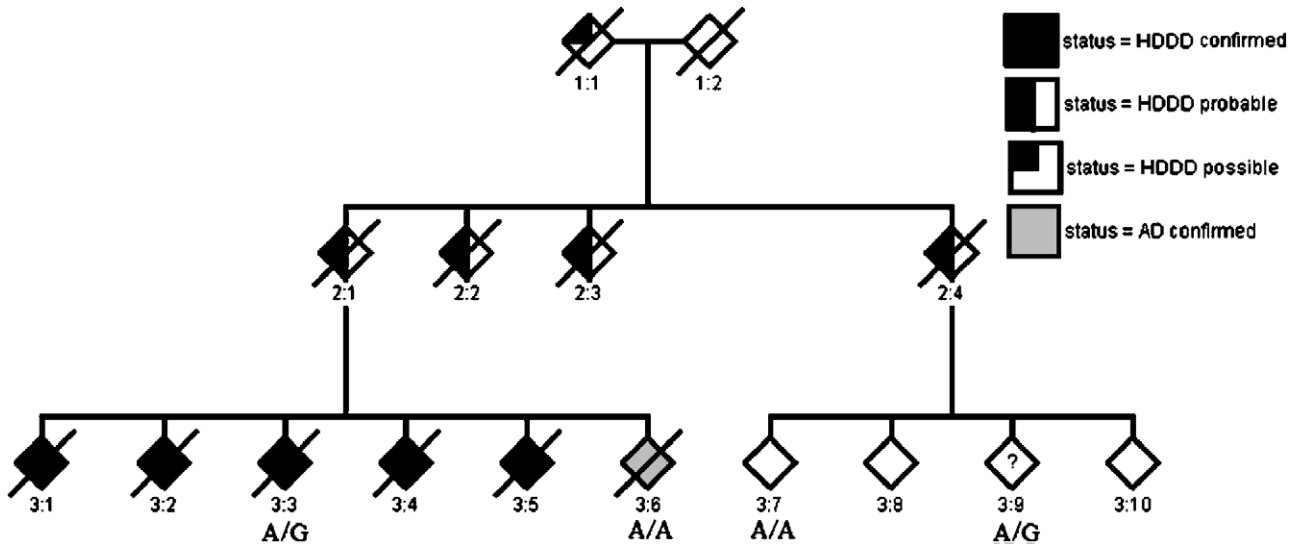

FIGURE 6. Segregation analysis of the splice site mutation c.5913 A>G (IVS6-2A>G) in the HDDD1 kindred. All information that could reveal the identity of members has been removed.

cases[1] but in contrast to the usual early involvement in typical AD.

Due to the presence of considerable Alzheimer-type pathology, the DNA was originally sequenced for the presence of *APP* mutations. In addition, *PS1* and *PS2* genes were sequenced because mutations in *PS1* gene have recently been described in familial FTLD,[16–21] including 2 cases associated with neuropathology compatible with Pick disease.[20,21] No mutations were found in these genes in the affected individual from HDDD1.

A subset of familial cases of FTLD is caused by mutations in the *tau* gene on chromosome 17.[22] Sequencing of exons 1 to 14 and the promoter of *tau* showed no mutations in the present case. Several other FTLD families show linkage to chromosome 17 but lack mutations in *tau*.[23–25] A linkage to chromosome 17 was observed in the HDDD2 kindred, a large family with a very similar clinical and pathologic phenotype as HDDD1.[2] After the discovery of *PGRN* mutations in other FTLD-U kindreds,[6] we recently identified a novel *PGRN* mutation in HDDD2.[7] Linkage studies were not feasible in the HDDD1 family due to the small size of the pedigree. Sequencing of the *PGRN* gene revealed a novel mutation, distinct from that causing HDDD2.

The co-occurrence of tauopathy in the form of NFT and extracellular Aβ plaques constitutes the pathologic definition of AD.[26] FTLD cases show variable degrees of tau deposits, and Aβ deposition is variable, most often correlated with an a*polipoprotein E* ε4 allele. The presence of both FTLD-motor neuron disease-type and AD pathology in HDDD1 may be a coincidence. It is also possible that there is a causal relationship between the 2 diseases, as supported by reports of the coexistence of FTLD and Aβ deposition.[27–30] Prominent NP deposition, sufficient to meet criteria for AD[9,31,32] has been reported in inherited FTDP-17. The autopsy of a patient (age at death 61 y) of the LKL pedigree with FTDP-17 showed both tau pathology and Aβ deposits. In 2 out of 7 cases of hereditary FTDs with *tau* mutations (ages 76 and 70 y old), Rosso et al[28] described diffuse and NPs. In another series of 54 autopsy cases of FTLD, Mann et al[29] reported that 14 cases (26%) had Aβ deposits. These patients were older at onset of illness than those without Aβ (mean onset age ± SD, 60.9 ± 8.5 y for those with Aβ, 54.9 ± 8.3 y for those without Aβ, $P < 0.025$). Lantos et al[30] found that in 3 of 12 cases of FTD with *tau* mutation in exon 10 + 16 there was coexisting AD pathology. An *apolipoprotein E* ε4 allele genotype was associated with the AD pathology,[29,30] which is consistent with the presence of an ε4 allele in the present case.

Of the other 4 members of the HDDD1 kindred described in the original report,[1] 3 had abundant Aβ deposition. The only case without Aβ deposition died at age 61 years (the age at death of the other cases was 66, 74, and 77 y). An acceleration of NFT formation due to Aβ deposition has been proposed in nondemented aging and preclinical AD,[31,32] and links between tau and Aβ deposition have been recently proposed.[33–35] It is speculated that mutant *tau* may result in Aβ deposition,[26] consistent with the observation that NFTs precede Aβ deposits in the entorhinal cortex in AD.[10,36,37] A recent report found a 2-fold increase of soluble intracellular Aβ42 and Aβ40 in FTDP-17 cases compared with normal or FTLD brains, suggesting that tau aggregation might induce an accumulation of Aβ.[35,38]

The identification of a mutation in the *PGRN* in HDDD1 links this family to other FTLD-U families in which *PGRN* mutations have been identified.[6–8] Although the frontal and temporal lobes are preferentially affected, there may be considerable variation in the type of ubiquitinated inclusions (NCI, DN, or NII) and their density, not only between members of the same kindred,

but also within the same brain. Studies are ongoing to determine the relationship between different *PGRN* mutations and clinical and neuropathologic heterogeneity.

ACKNOWLEDGMENTS

The authors thank Daniel W. McKeel, MD who contributed to the neuropathology of these cases and the HDDD1 family for making the research reported here possible. David S. Knopman, MD served as guest editor for this manuscript.

REFERENCES

1. Morris JC, Cole M, Banker BQ, et al. Hereditary dysphasic dementia and the Pick-Alzheimer spectrum. *Ann Neurol*. 1984;16: 455–466.
2. Lendon CL, Lynch T, Norton J, et al. Hereditary dysphasic disinhibition dementia: a frontotemporal dementia linked to 17q21-22. *Neurology*. 1998;50:1546–1555.
3. The Lund and Manchester Groups. Clinical and neuropathological criteria for frontotemporal dementia. *J Neurol Neurosurg Psychiatry*. 1994;57:416–418.
4. Neary D, Snowden JS, Gustavson L, et al. Frontotemporal lobar degeneration: a consensus on clinical diagnostic criteria. *Neurology*. 1998;51:546–1554.
5. McKhann GM, Albert MS, Grossman M, et al. Clinical and pathological diagnosis of frontotemporal dementia: report of the Work Group on Frontotemporal Dementia and Pick's Disease. *Arch Neurol*. 2001;58:1803–1809.
6. Baker M, Mackenzie IR, Pickering-Brown SM, et al. Mutations in progranulin cause tau-negative frontotemporal dementia linked to chromosome 17. *Nature*. 2006;442:916–979.
7. Mukherjee O, Pastor P, Cairns NJ, et al. HDDD2 is a familial frontotemporal lobar degeneration with ubiquitin-positive, tau-negative inclusions caused by a missense mutation in the signal peptide of progranulin. *Ann Neurol*. 2006;60:314–322.
8. Mukherjee O, Wang J, Gitcho M, et al. Prevalence and molecular characterization of *progranulin* mutations in frontotemporal lobar degeneration. *Hum Mol Genet*. (Unpublished data).
9. Hyman BT, Trojanowski JQ. Editorial on Consensus recommendations for the postmortem diagnosis of Alzheimer disease from the National Institute on Aging and the Reagan Institute Working Group on diagnostic criteria for the neuropathological assessment of Alzheimer disease. *J Neuropathol Exp Neurol*. 1997;56:1095–1097.
10. Braak H, Braak E. Neuropathological staging of Alzheimer-related changes. *Acta Neuropathol*. 1991;82:239–259.
11. Kertesz A, Munoz DG, Hillis A. Preferred terminology. *Ann Neurol*. 2003;54:S3–S6.
12. Bigio EH, Johnson NA, Rademaker AW, et al. Neuronal ubiquitinated intranuclear inclusions in familial and non-familial frontotemporal dementia of the motor neuron disease type associated with amyotrophic lateral sclerosis. *J Neuropathol Exp Neurol*. 2004;63:801–811.
13. Toyoshima Y, Piao YS, Tan CF, et al. Pathological involvement of the motor neuron system and hippocampal formation in motor neuron disease-inclusion dementia. *Acta Neuropathol*. 2003;106: 50–56.
14. Cairns NJ, Brannstrom T, Khan MN, et al. Neuronal loss in familial frontotemporal dementia with ubiquitin-positive, tau-negative inclusions. *Exp Neurol*. 2003;181:319–312.
15. Forno LS, Langston JW, Herrick MK, et al. Ubiquitin-positive neuronal and tau 2-positive glial inclusions in frontotemporal dementia of motor neuron-type. *Acta Neuropathol*. 2002;103:599–606.
16. Raux G, Gantier R, Thomas-Anterion C, et al. Dementia with prominent frontotemporal features associated with L113P *presenilin 1* mutation. *Neurology*. 2000;55:1577–1578.
17. Rogaeva EA, Fafel KC, Song YQ, et al. Screening for PS1 mutations in a referral-based series of AD cases: 21 novel mutations. *Neurology*. 2001;57:621–625.
18. Tang-Wai D, Lewis P, Boeve B, et al. Familial frontotemporal dementia associated with a novel presenilin-1 mutation. *Dement Geriatr Cogn Disord*. 2002;14:13–21.
19. Amtul Z, Lewis PA, Piper S, et al. A presenilin 1 mutation associated with familial frontotemporal dementia inhibits gamma-secretase cleavage of APP and notch. *Neurobiol Dis*. 2002;9:269–273.
20. Dermaut B, Kumar-Singh S, Engelborghs S, et al. A novel *presenilin 1* mutation associated with Pick's disease but not beta-amyloid plaques. *Ann Neurol*. 2004;55:617–626.
21. Halliday GM, Song YJ, Lepar G, et al. Pick bodies in a family with presenilin-1 Alzheimer's disease. *Ann Neurol*. 2005;57:139–143.
22. Hutton M, Lendon CL, Rizzu P, et al. Association of missense and 5′-splice-site mutations in tau with the inherited dementia FTDP-17. *Nature*. 1998;393:702–705.
23. Tolnay M, Probst A. Frontotemporal lobar degeneration-tau as a pied piper? *Neurogenetics*. 2002;4:63–75.
24. Rademakers R, Cruts M, Dermaut B, et al. Tau negative frontal lobe dementia at 17q21: significant fine mapping of the candidate region to a 4.8cM interval. *Mol Psychiatry*. 2002;7:1064–1074.
25. Rosso SM, Kamphorst W, de Graaf B, et al. Familial frontotemporal dementia with ubiquitin-positive inclusions is linked to chromosome 17q21-22. *Brain*. 2001;124:1948–1957.
26. Jellinger KA, Bancher C. Neuropathology of Alzheimer's disease: a critical update. *J Neural Transm Suppl*. 1998;54:77–95.
27. D'Souza I, Poorkaj P, Hong M, et al. Missense and silent *tau* gene mutations cause frontotemporal dementia with parkinsonism-chromosome 17 type, by affecting multiple alternative RNA splicing regulatory elements. *Proc Natl Acad Sci USA*. 1999;96:5598–5603.
28. Rosso SM, Kamphorst W, Ravid R, et al. Coexistent tau and amyloid pathology in hereditary frontotemporal dementia with tau mutations. *Ann N Y Acad Sci*. 2000;920:115–119.
29. Mann DMA, McDonagh AM, Pickering-Brown SM, et al. Amyloid β protein deposition in patients with frontotemporal lobar degeneration: relationship to age and *apolipoprotein E* genotype. *Neurosci Lett*. 2001;304:161–164.
30. Lantos PL, Cairns NJ, Khan MN, et al. Neuropathologic variation in frontotemporal dementia due to the intronic tau 10(+16) mutation. *Neurology*. 2002;58:1169–1175.
31. Khachaturian ZS. Diagnosis of Alzheimer's disease. *Arch Neurol*. 1985;42:1097–1105.
32. Mirra SS, Heyman A, McKeel D, et al. The Consortium to establish a registry for Alzheimer's disease (CERAD) II. Standardization of the neuropathologic assessment of Alzheimer's disease. *Neurology*. 1991;41:479–486.
33. Gamblin TC, Chen F, Zambrano A, et al. Caspase cleavage of tau: linking amyloid and neurofibrillary tangles in Alzheimer's disease. *Proc Natl Acad Sci U S A*. 2003;100:10032–10037.
34. Baki L, Shioi J, Wen P, et al. PS1 activates PI3K thus inhibiting GSK-3 activity and tau overphosphorylation: effects of FAD mutations. *EMBO J*. 2004;23:2586–2596.
35. Dermaut B, Kumar-Singh S, Rademakers R, et al. Tau is central in the genetic Alzheimer-frontotemporal dementia spectrum. *Trends Genet*. 2005;21:664–672.
36. Price JL, Morris JC. Tangles and plaques in nondemented aging and "preclinical" Alzheimer's disease. *Ann Neurol*. 1999;45:358–368.
37. Price JL, Morris JC. So what if tangles precede plaques? *Neurobiol Aging*. 2004;25:721–723.
38. Vitali A, Piccini A, Borghi R, et al. Soluble amyloid beta-protein is increased in frontotemporal dementia with tau gene mutations. *J Alz Dis*. 2004;6:45–51.

