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High Prevalence of Pathogenic Mutations in Patients with Early-Onset Dementia Detected by Sequence Analyses of Four Different Genes

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Summary

Clinical differential diagnosis of early-onset dementia (EOD) includes familial Alzheimer disease (FAD) and hereditary prion disease. In both disease entities, postmortem brain histopathological examination is essential for unambiguous diagnosis. Mutations in the genes encoding the presenilins (PS1 and PS2) and amyloid precursor protein (APP) are associated with FAD, whereas mutations in the prion protein (PrP) gene are associated with prion disease. To investigate the proportion of EOD attributable to known genes, we prospectively (i.e., antemortem) screened these four genes for mutations by sequencing genomic PCR products from patients with EOD before age 60 years. Family history for dementia was positive (PFH) in 16 patients, negative (NFH) in 17 patients, and unknown (UFH) in 3 patients. In 12 patients, we found five novel mutations (in PS1, F105L; in PS2, T122P and M239I; and in PrP, Q160X and T188K) and five previously reported mutations (in APP, in three patients who were most likely unrelated, V717I; in *PS1*, A79V and M139V; and in PrP, P102L and T183A) that are all considered to be disease causing. Of these 12 patients, 9 had PFH. This indicates a detection rate of 56% (9/16) in patients with PFH. We found two mutations (APP V717I) in two of the three UFH patients, and only one mutation (PrP T188K) in 1 of the 17 patients with NFH. We conclude that because of the lack of specific antemortem diagnostic markers for FAD and hereditary prion disease, all four genes should be included in a molecular diagnostic program in patients with EOD who had PFH.

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Introduction

Heterozygous mutations in the presenilin genes (*PSEN1*, *PSEN2*) and in the amyloid precursor protein gene (*APP*) may cause early-onset autosomal-dominant familial Alzheimer disease (FAD) (MIM 104300) (Goate et al. 1991; Levy-Lahad et al. 1995; Rogaev et al. 1995; Sherrington et al. 1995). Clinical manifestation in Alzheimer disease (AD) is variable (Mayeux et al. 1985), and differential diagnosis of early-onset dementia (EOD) may include, in addition to FAD, prion disease (MIM 176640) associated with mutations in the prion protein gene (*PRNP*) but lacking the classical neurological signs of Creutzfeldt-Jakob disease (CJD) (MIM 123400) (Haltia et al. 1994; Geldmacher and Whitehouse 1997; Hardy and Gwinn-Hardy 1998). Clinical manifestation also is variable in hereditary prion disease, particularly in Gerstmann-Sträussler-Scheinker disease (GSS) (MIM 137440) (Hainfellner et al. 1995; Hamasaki et al. 1998). In both AD and prion disease, neurodegeneration is accompanied by cerebral deposits of amyloid and aggregated tau neurofibrils. The lack of specific and unambiguous clinical or biochemical antemortem diagnostic markers for both entities leads to difficult diagnostic situations in dementia patients without significant neurological signs in the early disease stage, and postmortem histopathological evaluation is necessary for confirmation of the clinical diagnosis.

In genetically relatively isolated populations, a small number of FAD mutations have been observed repeatedly, for example, PS2 N141I in Volga Germans (Rogaev et al. 1995), PS1 A79V in the Dutch population (Cruts et al. 1998), and PS1 H163R in the Japanese population (Kamimura et al. 1998), which may be explained by founder effects. To determine the spectrum of mutations and the relative contribution of the previously mentioned four genes, we performed a prospective molecular diagnostic program in an ethnically heterogeneous group of patients with EOD and no significant early neuro-

logical signs. Such a study may help to establish criteria for molecular diagnostics in dementia.

Subjects and Methods

DNA Samples

Genomic DNA was prepared from peripheral blood leukocytes of 36 unrelated German, Austrian, Italian, Hungarian, and Swiss patients with EOD and onset before age 60 years, and 3 unrelated German patients with late-onset dementia after age 65 years. None of the patients had significant neurological signs in the early disease stage, and all had a clinical diagnosis of dementia of unknown type or possible or probable AD. Sixteen of the EOD patients had positive family history (PFH) of EOD, whereas the 3 late-onset patients had PFH of late-onset dementia. PFH was assumed if at least one first-degree relative with dementia was reported. In some cases, material from siblings or parents was available for molecular analysis. DNA or blood from a total of 15 patients was sent directly to our laboratory from clinical centers or general practitioners. Twenty-four patients were ascertained by AD research centers (22 in Hamburg, Germany and 2 in Brescia, Italy). Most of the patients seen outside our laboratory and all research-study patients underwent full medical and neurological examinations, cognitive evaluations, routine blood tests, EEGs, and brain computed tomography (CT) scans. Clinical diagnosis of possible or probable AD was made according to criteria of the National Institute of Neurological and Communicative Disorders and Stroke and Alzheimer's Disease and Related Disorders Associations (McKhann et al. 1984). Postmortem histopathological analysis in index patients (2, 7, and 13) was performed according to the criteria recommended by the Consortium to Establish a Registry for the Diagnosis of Alzheimer's Disease (Mirra et al. 1991). Ethical approval for this study was obtained from local ethics committees. Research-study patients (if possible) and their caregivers gave informed consent to participate.

Sequencing and Genotyping

Mutation analysis was done on genomic DNA by direct sequencing of both strands of PCR-amplified coding exons of *PSEN1, PSEN2,* exons 16 and 17 of *APP,* and the single coding exon of *PRNP.* Primer sequences were designed according to GenBank entries and are available on request. Amplification was done by a universal "touch down" protocol, and amplicons were sequenced by fluorescent dye dideoxy terminators, as described elsewhere (Finckh et al. 1998). Mutation screening was stopped if a known and most likely disease-causing mutation was identified in any patient. In all other patients, all four previously mentioned genes were analyzed. All sequence changes were confirmed by restriction-enzyme digestion or allele-specific PCR (ASP) (table 1). *PRNP* haplotypes were determined by selective sequencing of single alleles after restriction digestion at polymorphic codon 102 (Owen et al. 1989).

Results

In 14 patients, we found a total of 12 different mutations in *PSEN1, PSEN2, APP,* and *PRNP* (fig. 1 and table 1). Of the 12 mutations, 5 were previously undescribed and 7 were known. None of the five novel mutations were present on $\geqslant$100 control chromosomes. Of the 12 mutations reported here, 2 (PS1 E318G, PrP del r34) are considered nonpathogenic polymorphisms (see following). The 10 remaining mutations, in a total of 12 patients, affect evolutionarily highly conserved residues. Of these 12 patients, 9 had PFH of EOD (fig. 1 and table 2). No mutation was found in the four genes studied in the three patients with late-onset dementia and PFH for late-onset dementia.

PS1 A79V

Age at onset was ~58 years in patient 1. The disease course was initially mild: she retired from work at age 60 years and lived in her own house until age 72 years, when she was admitted to a nursing home. Since age 77 years, she has been bedridden. At age 78 years, there is severe dementia. A similar age at onset and a 10-year duration of the disease were reported for the patient's mother. Several maternal relatives were said to be affected by EOD. However, no written reports were available. Several Dutch FAD cases with the PS1 A79V mutation, most likely the result of a common founder, and a clinical course similar to that of our patient have been reported recently (Cruts et al. 1998).

PS1 F105L

This novel *PSEN1* mutation was found in patient 2, whose age at onset of disease was 52 years. Residue 105 is in the hydrophilic loop 1, immediately adjacent to transmembrane domain 1 of PS1. The diagnosis of probable AD was first documented at age 59 years, when her mini-mental state-examination (MMSE) (Folstein et al. 1975) score was 13 of 30. At age 60 years, she developed Parkinson-like symptoms. She died in a fully demented and bedridden state at age 63 years. Autopsy of the brain excluded Parkinson disease and confirmed the suggested diagnosis of AD by demonstration of numerous neurofibrillary tangles (NFT) and senile plaques (SP) in hippocampus in addition to disseminated cortical SP. EOD was reported both for the mother and maternal grandmother of the patient.

Table 1

Mutations Found in 14 Patients with EOD

Patient	Origin[a]	DNA Mutation	Predicted Protein Alteration	Mutation Confirmation[b]	Family History[c]	Onset[d]	Cosegregation[e]
1	G	GCC→GTC	PS1 A79V	−*Hha*I	Early	~58	NA
2	G	TTT→TTG	PS1 F105L[f]	+*Bst*1107 I	Early	~52	NA
3	G	ATG→GTG	PS1 M139V	−*Nla*III	Early	32	NA
4	G	GAA→GGA	PS1 E318G[g]	ASP	Negative	53	ND
5	G	GAA→GGA	PS1 E318G[g]	ASP	Late	53	NA
6	G	ACG→CCG	PS2 T122P[f]	−*Aci*I	Early	46	+
		del 24bp	PrP del r34[h]	Sequencing			−
7	I	ATG→ATA	PS2 M239I[f]	−*Hae*III	Early	58	+
8	G	GTC→ATC	APP V717I	+*Bcl*I	Early	~50	NA
9	G	GTC→ATC	APP V717I	+*Bcl*I	Unknown	53	ND
10	T	GTC→ATC	APP V717I	+*Bcl*I	Unknown	54	ND
11	G	CCG→CTG	PrP P102L	+*Dde*I	Early	40	+
12	A	CAA→TAA	PrP Q160X[f]	+ *Dde*I	Early	32	+
13	G	ACA→GCA	PrP T183A	ASP	Early	40	+
14	A	ACG→AAG	PrP T188K[f]	ASP	Negative	59	ND

[a] G = Germany; T = Thailand; I = Italy; A = Austria.

[b] Confirmation of mutation by restriction endonuclease digestion (+ / − = gain / loss of cleavage site, respectively) or allele-specific PCR (ASP).

[c] Early = EOD; late = late-onset dementia reported in first-degree relatives of the index patient; unknown = family history unknown or not informative; negative = family history negative for dementia.

[d] Age at onset of dementia in index patient.

[e] NA = No family material available for segregation analysis; ND = unknown or negative family history; + = cosegregation; − = no cosegregation of EOD with the mutation.

[f] Mutation not described previously.

[g] This mutation affects an evolutionarily-not-conserved residue, and it seems to be a nonpathogenic polymorphism.

[h] This in-frame deletion seems to be a nonpathogenic polymorphism.

PS1 M139V

This *PSEN1* mutation was found in patient 3, whose age at onset of disease was 32 years. At age 39 years, various neurological symptoms—including extrapyramidal hyperkinetic movement disorders, ataxia, and incontinence—were documented, and she was admitted to a nursing home. From age 40 years, she needed a wheelchair and had grand mal epileptic seizures. At age 45 years, she is bedridden and presents akinetic mutism, a virtually apallic syndrome, spastic tetraplegia, and frequent myoclonic jerks. This severe disease course is similar to those reported previously for other patients carrying M139V (Fox et al. 1997; Hull et al. 1998). Both the patient's father and paternal grandfather died in a demented state at age 41 years and 46 years, respectively, and for both, an autopsy-based histopathological confirmation of AD was reported by demonstration of SP and NFT.

PS1 E318G

This nonsynonymous *PSEN1* change was found in two patients (4, 5) with negative family history for EOD. The father of one of the patients had late-onset dementia. PS1 E318G seems to be a nonpathogenic polymorphism of an evolutionarily-not-conserved residue that has repeatedly been found in nondemented control subjects (Aldudo et al. 1998; Mattila et al. 1998; Dermaut et al. 1999). In line with this assumption, and in contrast to other *PSEN1* mutations, E318G was shown not to affect beta-catenin trafficking (Nishimura et al. 1999).

PS2 T122P

This *PSEN2* mutation was identified in patient 6, whose age at onset of disease was 46 years. She retired from work at age 47 years. At age 49 years, she had an MMSE score of 16, and the clinical diagnosis of probable AD was presented. The observed clinical course was similar to that of her mother and her maternal grandmother, who died at ages 48 years and 51 years, respectively. The mutation was not found in her healthy (at age 81 years) father. Family history suggests a constant pattern of phenotype expression and a high penetrance of T122P unlike M239I (see following) and the previously reported mutations N141I and M239V of *PSEN2* (Levy-Lahad et al. 1995; Rogaev et al. 1995).

PrP del r34

In addition to the PS2 T122P mutation, patient 6 carried a heterozygous 24-bp in-frame deletion in *PRNP* (del r34). This deletion removes part of the last two of

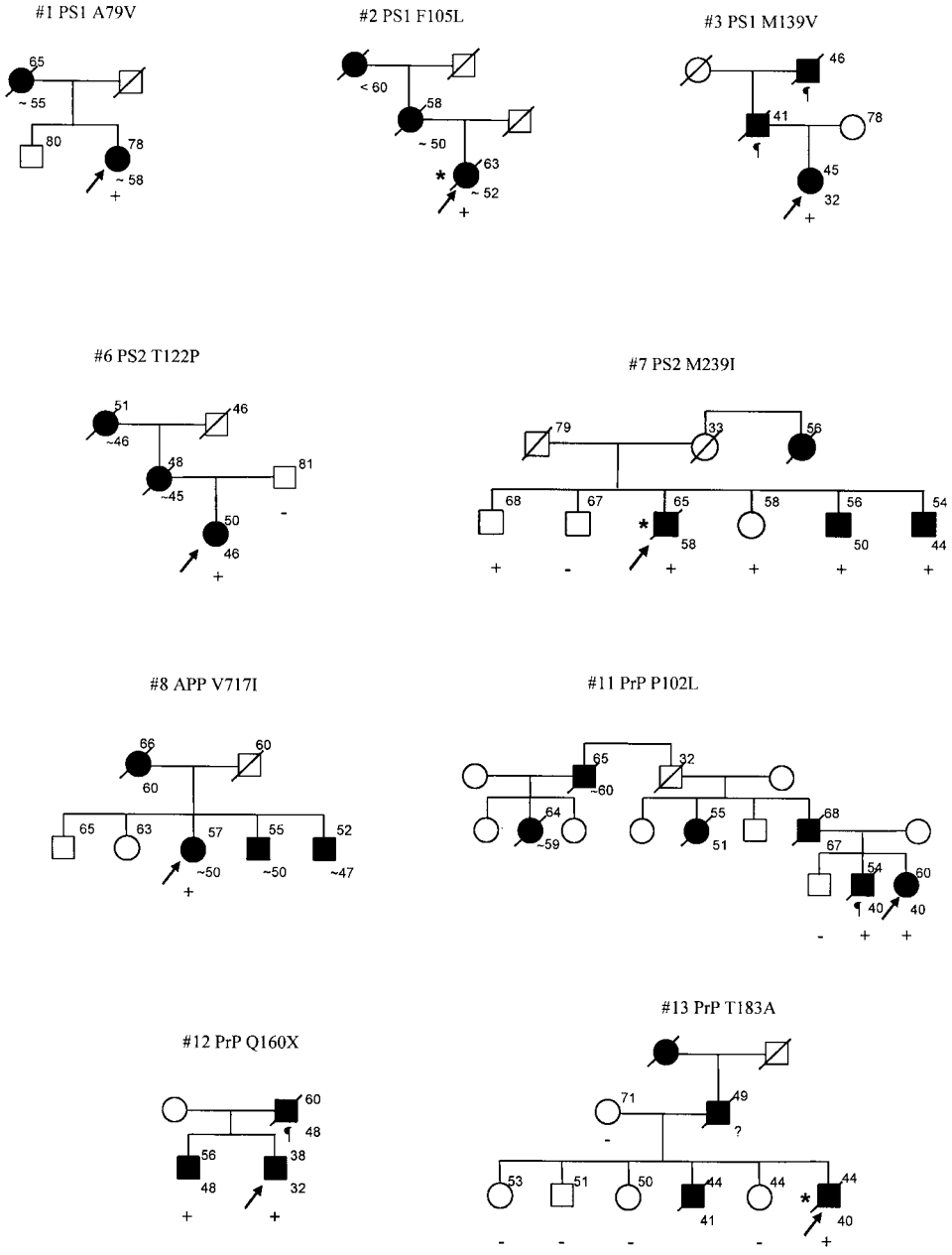

Figure 1 Pedigrees of the families with history of EOD and most likely pathogenic mutations described in this study. Numbers above the pedigree symbols indicate actual age or age at death. Numbers below the filled symbols indicate the probable age at onset in index patients (*arrow*) or their affected relatives. Results of mutation screening on the samples available for molecular analyses are indicated as + (mutation found) and − (mutation excluded) below the pedigree symbols. Available histopathological autopsy results of index patients are indicated by an asterisk (*). Reports about previous histopathological analyses in affected relatives are indicated by a pilcrow (¶).

the five proline-rich octapeptide repeat elements (r1-r2-r2-r3-r4) in PrP (Kretzschmar et al. 1986). In patient 6, del r34 was in *cis* with the M129-encoding allelic variant of PrP 129M/V (Owen et al. 1989). As a result of the high sequence similarity of the repeat elements, it is impossible to determine the precise location of the deletion that may be identical to previously reported *PRNP* deletions found both in patients with dementia and in non-demented subjects (Palmer et al. 1993; Perry et al. 1995; for literature, see also "The Official Mad Cow Disease Home Page"). Both the patient and her father were heterozygous for M129V. The patient's father, who was not demented at age 81 years and did not carry the PS2 mutation, also carried M129 in *cis* with del r34. There-

Table 2

Frequency of Pathogenic Mutations Detected in 39 Unrelated Patients with Dementia Grouped According to Onset and Family History

Clinical Diagnosis of Index Patient	Family History	*n*	Pathogenic Mutations
EOD	EOD	16	9
	Negative for EOD	17	1
	Unknown	3	2
Late-onset dementia	Late-onset dementia	3	0

fore, del r34 is likely a nonpathogenic polymorphism. This conclusion is supported by a report on cosegregation of dementia with PS1 H163R but not with a 24-bp *PRNP* deletion in two siblings with mixed neuropathological features of AD and CJD (El Hachimi et al. 1996).

PS2 M239I

We have identified another yet-undescribed *PSEN2* mutation (M239I in PS2 TM5) in the index patient (patient 7) of an Italian family with three affected siblings. Patient 7 had a mild disease course with onset at age 58 years. He died, at age 65 years, of a ruptured aortic aneurism. AD was histopathologically confirmed at autopsy. In this family, five siblings carried PS2 M293I, but only three of them had AD. Both unaffected mutation carriers are at least as old as their affected siblings (fig. 1) and are considered to be at risk for later-onset dementia. The two younger affected siblings of patient 7 have a more severe course and earlier onset (U. Finckh, unpublished data). This phenotypic variability is similar to that of the previously reported PS2 mutations M239V in an Italian and N141I in Volga German kindreds (Levy-Lahad et al. 1995; Rogaev et al. 1995; Bird et al. 1996; Sherrington et al. 1996).

APP V717I

In three most likely unrelated patients with dementia (patients 8–10), we identified the "London" mutation APP V717I (Goate et al. 1991). Patient 8, with PFH and onset at ~50 years of age, had an MMSE score of 3 at age 57 years, when her CT scan revealed a marked brain atrophy that was most pronounced in the temporal lobes and without signs of ischemic infarctions. No family material was available (fig. 1). Patient 9, with onset at age 53 years, has an MMSE score of 25 at age 56 years. His parents had no dementia, but died before age 50 years. Family history was unavailable. Patient 10, with a probable dementia onset at age 54 years, has an MMSE score of 14 at age 56 years. She is a Thai immigrant to Germany and no detailed information about her family history was available.

PrP P102L

This mutation in *PRNP* codon 102 was found in two siblings, both with onset at age 40 years. Both siblings shared the GSS haplotype PrP L102 in *cis* with M129 (Hsiao et al. 1989; Hainfellner et al. 1995), and were heterozygous for M/V at codon 129. At age 43 years, the affected brother of the index patient had a diagnostic antemortem brain biopsy of the right prefrontal cortex. Histopathologically (staining techniques: HE, trichrom. Masson, PAS, Bielschowsky) were found some atrophic neurons, multiple small and larger-sized amorphic amyloid areas with only few glial reactions surrounding them, and neurofibrillary aggregates in some single neurons. The white matter was described as spongious, with some areas of discrete reactive glial proliferation. All of these together were interpreted as signs of primary cortical atrophy of Alzheimer type. The patient died at age 54 years; no autopsy was done. Analysis of the pedigree revealed several relatives with ataxia and largely variable clinical phenotype characteristic for GSS.

PrP Q160X

In an Austrian family, we identified the novel nonsense mutation PrP Q160X. This mutation, in *cis* with PrP M129, was found both in the index patient (patient 12), with onset of dementia at age 32 years and a severe and rapidly progressing course, and in his elder brother, with onset at age 48 years and a mild course. The wild-type allele of the younger brother encodes M129 and that of the elder brother encodes V129. Repeated EEGs from patient 12 done at at ages 35, 36, 37, and 38 years were slightly abnormal, with diffuse theta increment and intermittent theta groups but without hints of seizures. Both cranial CT at age 35 years and magnetic-resonance imaging (MRI) at age 37 years showed severe ventricular and sulcal enlargement. Cranial MRI of the elder brother, done at age 55 years, showed almost normal findings with only slight cerebellar atrophy. So far, after disease durations of 6 and 8 years, respectively, no neurological sign of CJD or ataxia has been observed in the two brothers. Their father also had dementia with onset at age 48 years and a severe course resembling that of the index patient. The father died with pneumonia at age 60 years. Pathology reports from 1980 noted a reduced brain weight of 1,200 g, diffuse cortical atrophy, extensive enlargement of ventricles, little arteriosclerosis of brain vessels, and no stenosis of the carotid arteries. No microscopic analyses were done.

PrP T183A

Patient 13 represents the second case with this mutation first described in a Brazilian family with EOD and histopathologically confirmed spongiform encephalo-

pathy (Nitrini et al. 1997). The clinical course in patient 13 was observed over a period of 4 years. Because there were no neurological signs of CJD, the clinical diagnosis of possible AD was made. The patient died at age 44 years, and autopsy confirmed hereditary prion disease by demonstration of spongiform encephalopathy (U. Mann, unpublished data).

PrP T188K

We discovered this novel missense mutation in *PRNP* codon 188 in a 59-year-old patient (patient 14) with a NFH. Initially, leading signs of the disease were dysphasia along with dementia. In this patient, the disease is rapidly progressing and has reached a most severe dementia in <1 year.

Discussion

Mutation Detection Rates

The results summarized in this report, together with those of other authors, suggest that 10 of the 12 different mutations detected in 14 of a total of 36 patients with EOD are disease causing. Our data indicate a high prevalence of pathogenic mutations in *APP, PSEN1, PSEN2,* or *PRNP* in patients with onset of dementia at age <60 years and PFH of EOD. Of the 16 patients with PFH, 9 (56%) carried pathogenic mutations, whereas only 1 of 17 patients with NFH carried a pathogenic mutation that was in *PRNP* (see table 2). The latter patient also has clinical signs atypical of AD, and he most likely has prion disease.

The high frequency of mutations in the three known FAD genes of patients with PFH extends the data obtained in Dutch and Japanese FAD studies that reported detection rates by PCR-SSCP of 18% and 20%, respectively (Cruts et al. 1998; Kamimura et al. 1998). In these studies, only *PSEN1* mutations—and no mutations in *PSEN2* or *APP*—were found. In the relatively homogeneous Dutch and Japanese populations, the frequency and spectrum of disease mutations may be different from that of a more heterogeneous population. This view is supported by the recurrent finding of PS1 A79V in the Dutch population, pointing to a possible founder effect (Cruts et al. 1998) and the repeated finding of PS1 H163R in the Japanese population (Kamimura et al. 1998). The data from our multinational patient sample suggest an extensive genetic heterogeneity of FAD. Furthermore, our data suggest that, in a well-selected group of patients, over 50% of the genetic causes of EOD resembling FAD, or 46% of early-onset FAD, can be readily identified.

PRNP versus FAD Mutations

Patients with dementia who had mutations in *PSEN1*, *PSEN2,* or *APP* most likely have FAD, whereas mutations in *PRNP* lead most likely to prion disease. In all three deceased index patients of our prospective study, molecular prediction was confirmed histopathologically at autopsy. An affected sibling of one of our index patients (11) with the well-known GSS mutation, PrP P102L, had a biopsy-based histopathological diagnosis of AD in 1987, 2 years before the first report on a familial PrP mutation appeared (Hsiao et al. 1989). In up to 10% of histopathologically confirmed CJD cases, AD-typical neuropathologic changes can also be seen (Hainfellner et al. 1998). So the limited amount of antemortem brain biopsy material available and the lack of PrP-specific immunocytochemistry may explain the interpretation of the findings as AD in this patient.

The observation of 4 mutations in *PRNP*, among a total of 12 pathogenic mutations in patients with EOD, suggests an important overlap in clinical symptoms between FAD and hereditary prion disease. Together with the findings of other studies that prion disease and AD pathology may be present simultaneously (El Hachimi et al. 1996; Hainfellner et al. 1998), our data support the idea that AD and prion disease may occur jointly in individual patients.

PrP Q160X

The M/V polymorphism at PrP residue 129 is known to modify phenotype expression of several prion disease alleles (Goldfarb et al. 1992; Barbanti et al. 1996; Young et al. 1997). A premature stop of *PRNP* at codon 145 (Y145X) was previously found in an isolated case with unknown family history and a clinical diagnosis of AD but with a postmortem diagnosis of cerebral PrP amyloid angiopathy (Kitamoto et al. 1993; Ghetti et al. 1996). RT-PCR results (Kitamoto et al. 1993) and protein data (Ghetti et al. 1996) suggested expression of the mutated allele and its involvement in cerebral PrP pathology. For Q160X, however, we assume an analogy that cannot be investigated in vivo in the two brothers carrying this mutation. However, our finding of the nonsense mutation in both brothers and the PFH strongly support the view that a PrP stop mutation may well be causative in autosomal-dominant dementia.

Conclusions

The data presented in this study show the importance of diagnostic sequencing of *APP, PSEN1, PSEN2,* and *PRNP* in patients with EOD and PFH but without neurological signs in the early phase of the disease and without histopathological analysis. So as not to miss specific treatments of known causes of dementia, and for proper

clinical and genetic counseling, early and disease-specific diagnosis of EOD is essential. This need will be even more urgent with the upcoming more efficient or even preventive specific treatment of AD or prion disease.

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Electronic-Database Information

URLs for data in this article are as follows:

GenBank, http://www.ncbi.nlm.nih.gov/Genbank/GenbankOverview.html
Official Mad Cow Disease Home Page, The, http://mad-cow.org/~tom
Online Mendelian Inheritance in Man (OMIM), http://www.ncbi.nlm.nih.gov/Omim/

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