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SHORT REPORT

Novel presenilin-1 mutation with widespread cortical amyloid deposition but limited cerebral amyloid angiopathy

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Abstract

Objective—To clarify the phenotypic heterogeneity in deposition of amyloid beta (A β) in the parenchyma and in cerebral vessels of the brains of the patients having presenilin-1 (PS1) mutations. Mutations in PS1 induce increased production of A β 42(43), resulting in an enhanced overall deposition of A β protein within the cerebral cortex.

Methods—Sequence analysis of the PS1 gene of DNA from patients with early onset Alzheimer's disease, and immunostaining of brain tissues by end specific monoclonal antibodies against A β .

Results—Sequence analysis disclosed a novel mutation (N405S) in the PS1 gene in a Japanese patient with early-onset Alzheimer's disease. Postmortem examination of one patient with N405S showed limited cerebral amyloid angiopathy, whereas postmortem examination of another Japanese patient with Alzheimer's disease with the E184D mutation disclosed severe cerebral amyloid angiopathy. The brains of both patients showed widespread neuritic plaques, neurofibrillary tangles, and neuronal loss. Immunostaining showed that A β 42 was predominant over A β 40 in neuritic plaques in both patients, whereas A β 40 was found to be predominant over A β 42 in cerebral amyloid angiopathy in the patient with E184D. However, most cortical vessels of the patient with N405S were not reactive with either of the antibodies.

Conclusion—The N405S mutation of PS1 is a major determinant of cortical A β deposition but not cerebral amyloid angiopathy in Alzheimer's disease.

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Keywords: presenilin-1; mutation; Alzheimer's disease; amyloid angiopathy

Most known early onset familial Alzheimer's disease pedigrees are linked to mutations in the presenilin-1 (PS1) gene on chromosome 14.¹ Mutations in PS1 have been demonstrated to alter the processing of amyloid precursor

protein in a manner leading to increased production of amyloid beta (A β)42(43) in plasma,² in brain tissues,^{2,3} in transfected cells,^{4,6} and in transgenic mice.⁴ The increase of A β 42 that is deposited selectively and early in Alzheimer's disease may result in an enhanced overall deposition of A β protein within the cerebral cortex.^{2,3} Thus, PS1 mutations can cause an aggressive form of early onset Alzheimer's disease. Postmortem examination of cases with PS1 mutations have been reported to have abundant cerebral amyloid angiopathy as well as many neuritic plaques.⁷ We also reported that an early onset Alzheimer's disease pedigree with E184D substitution has severe cerebral amyloid angiopathy.⁸ However, the extent of the A β 42 increase did not correlate with PS1 expression levels, and a similar increase was not found in the level of A β 40.^{2,3,5} Different PS1 mutations have different effects on A β generation, which may induce heterogeneity of clinicopathological features in PS1 associated Alzheimer's disease. We report in this study the detection of a novel mutation of the PS1 gene, N405S, in a Japanese patient with early onset Alzheimer's disease. Although postmortem examination of this patient showed widespread neuritic plaques, neurofibrillary tangles, and neuronal loss, there was occasional cerebral amyloid angiopathy. Comparison of the neuropathological features of patients with N405S and E184D emphasises the phenotypic heterogeneity in cerebral amyloid angiopathy.

Materials and methods

SUBJECTS

Early onset sporadic Alzheimer's disease in Kobe (case HI-1)

A housewife developed memory impairment and was unable to manage housework at the age of 48. The dementia syndrome rapidly progressed over the next year with apparent spasticity to eventually become akinetic mutism. The patient died at 53 years of age, and the diagnosis of Alzheimer's disease was confirmed at postmortem at Kobe University School of Medicine. She had no known familial background of dementia. Her father had died aged 69 with diabetes mellitus and her mother died

at the age of 75, and neither had dementia. Two other siblings, one elder sister and one younger brother, had no dementia.

We compared the pathological findings of the case of HI-1 with those of a patient of the ABCD-1 pedigree⁸ to clarify the phenotypic heterogeneity between the patients with PS1 mutations. The patient of the ABCD-1 pedigree was a man who developed memory impairment at the age of 44, myoclonus, and seizure, and died at the age of 51 years. The patient's mother and her other child had also developed dementia.

Genomic DNA was extracted from a block of brain tissue embedded in paraffin by using the conventional method.⁹ The target PS1 gene was sequenced as described previously.⁸ Apolipoprotein E (apoE) genotyping was performed according to the method of Wenham *et al.*¹⁰

Neuropathological examination

Sections from formalin fixed paraffin embedded brain tissues of the frontal, parietal, and temporal cortices, the hippocampus, amygdala, basal ganglia, thalamus, brainstem, and cerebellum were stained with haematoxylin-eosin, luxol fast blue-cresyl violet, and a modified Bielschowsky method. Selected sections were also immunostained for the two types of carboxyl terminus of A β proteins, A β 42(43) and A β 40, by using end specific monoclonal antibodies¹¹ BC05 and BA27, or using end specific affinity purified polyclonal antibodies (Quality Control Biochemicals, Inc, Hopkinton, MA, USA), β 40 for A β C-term40, and β 42 for A β C-term42,¹² after pretreatment with 99% formic acid for 5 minutes.

Results

MISSENSE MUTATION IN EXON 12 OF THE PS1 GENE (N405S)

The nucleotide and exon numberings described here are according to those of GenBank No L76518–76528. Compete sequencing of the PS1 gene of case HI-1 disclosed a new missense mutation (A to G) at nucleotide 1462 in exon 12, which is predicted to cause an asparagine to serine missense substitution at codon 405 (N405S) in the C terminus of the large loop of PS1. The substitution of A to G in the second position of codon 405 creates a restriction site for BpmI (fig 1). A polymerase chain reaction (PCR) restriction fragment length polymorphism analysis confirmed the heterozygote substitution at nucleotide 1462 of the PS1 gene. The same substitution was not found in 100 healthy control subjects or in 100 patients with sporadic Alzheimer's disease.

NEUROPATHOLOGY IN N405S MUTATION IN THE PS1 GENE

The clinical diagnosis of Alzheimer's disease was confirmed by the presence of many neuritic plaques and neurofibrillary tangles in the postmortem neuropathological study (fig 2 A). In addition, microscopical examination of brain tissues from HI-1 showed a considerable loss of nerve cells in the hippocampus (fig 2 A), entorhinal cortex, and amygdala. Neuronal loss was also evident in the cerebral neocortex. A

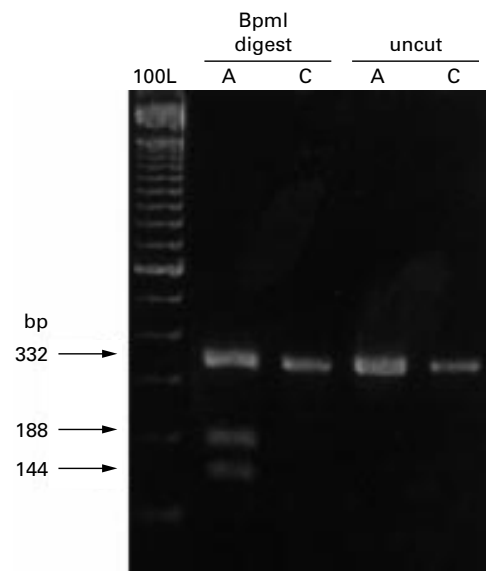


Figure 1 BpmI restriction enzyme analysis of the mutation at nucleotide 1462 (A to G) in a sporadic patient with early onset Alzheimer's disease without a known familial background of dementia (case HI-1). The amplification primers (forward: the Ex11-F primer, and reverse: the 893 primer) and polymerase chain reaction (PCR) conditions were as previously described.⁸ The normal PCR product is 332 base pairs (bp), which is not cleaved into any fragments. The patient was heterozygous for an A-to-G transition that creates a new restriction enzyme site for BpmI. When the PCR products were digested with BpmI and subsequently fractionated on 2% agarose (NuSieve 3:1; FMC, Rockville, USA) gel, this additional restriction site was shown by the appearance of novel bands corresponding to 188-bp and 144-bp fragments. C=control; A=affected; 100L=100 bp ladder (Gibco-BRL).

modified Bielschowsky silver impregnation technique identified numerous neuritic plaques, neuropil threads, and neurofibrillary tangles with severe gliosis in the hippocampus, entorhinal cortex, amygdala, and neocortical areas examined. Cerebral amyloid angiopathy was not as remarkable in the brain parenchyme of this case as it was in the affected brain tissues of the ABCD-1 family with the E184D mutation (fig 2 B).⁸

The two A β 40 antibodies or the two A β 42 antibodies exhibited a similar pattern of immunostainings, respectively. Immunohistochemistry of temporal cortices from the HI-1 and the ABCD-1 cases for A β 40 or A β 42(43) disclosed that BC05 or β 42 positive neuritic plaques containing A β 42(43) peptide were predominant over BA27 or β 40 positive plaques containing A β 40 peptide as in the case of the patient with sporadic Alzheimer's disease,¹¹ but the predominance was not as remarkable as that reported in the familial Alzheimer's disease cases with the amyloid precursor protein 717 mutation (fig 2 C-F). In the hippocampus of the patient with familial Alzheimer's disease in the ABCD-1 family, there was a prominent cerebral amyloid angiopathy (fig 2 E-H), which was preferentially immunoreactive for A β 40 (fig 2 F and H). By contrast, immunolabelling of cerebral vessels was not found either for A β 42(43) or for A β 40 (fig 2 C and D) in the affected brain tissues of the HI-1 case. Thus, the immunohistochemistry showed that A β 42(43) was predominant

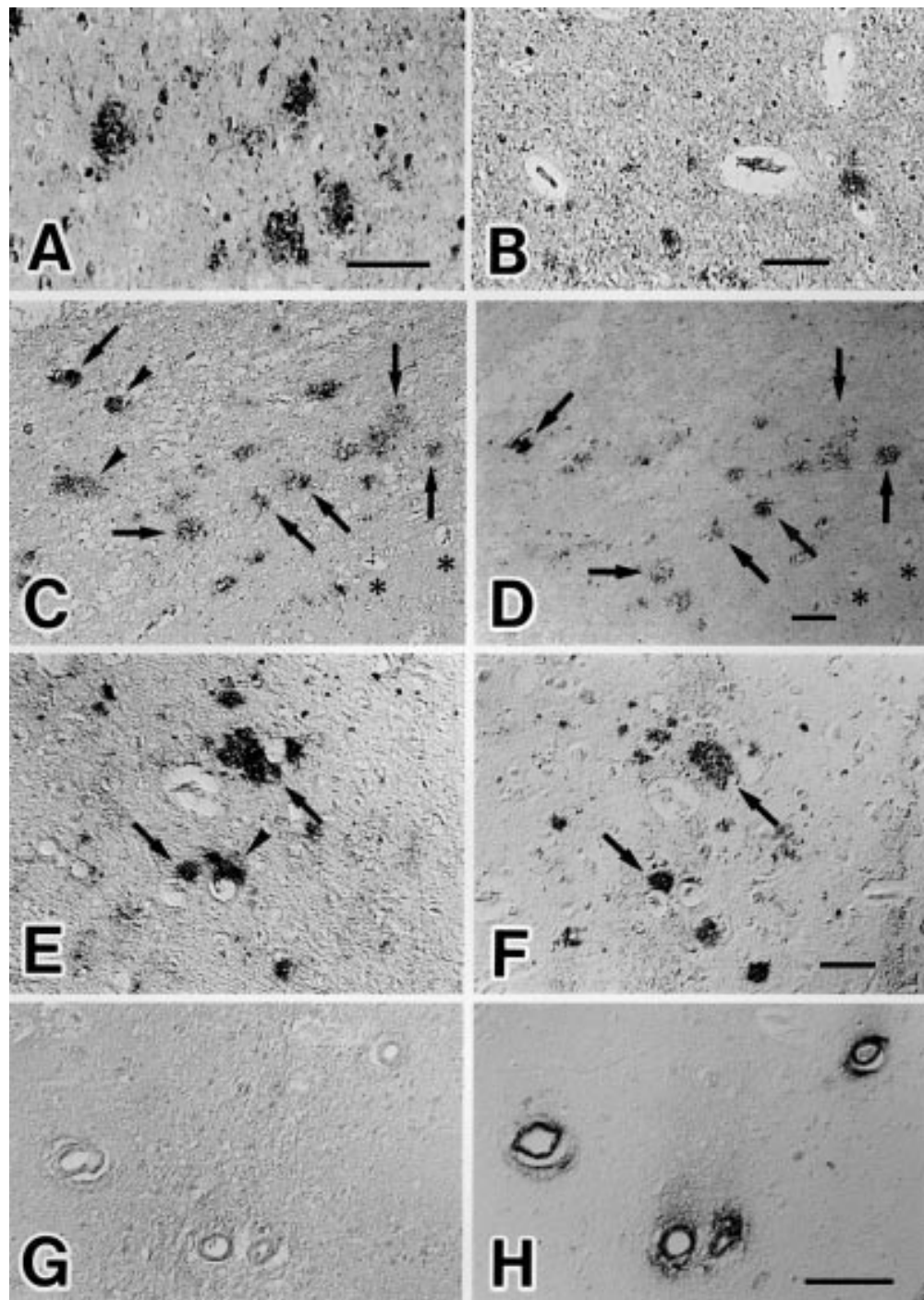


Figure 2 Neuropathology of the temporal cortices from HI-1 (A-D) and ABCD-1 (E-H) cases. Note many neuritic plaques, neurofibrillary tangles, neuropil threads, and neuronal loss (A), and a few areas of cerebral amyloid angiopathy (B) in the hippocampus of the HI-1 case. In C-H, two neighbouring sections were immunostained with BC05 or anti-A β 42 (C, E, and G) and BA27 or anti-A β 40 (D, F, and H) antibodies recognising A β 42(43) and A β 40, respectively. Note that BA27 immunolabelled only a subset of the neuritic plaques stained with BC05. In the temporal cortices of the patients of the HI-1 or the ABCD-1 pedigrees, numerous BC05 positive neuritic plaques (arrowheads in C and E) were not labelled with BA27 (D and F), whereas some plaques were doubly stained (arrows in C-F). In the temporal cortex from the HI-1 case, where amyloid angiopathy was not remarkable, most vessels were not reactive with either of the antibodies (asterisks in C and D). BA27 labelled more amyloid bearing vessels than BC05 in the ABCD-1 case (G and H). Most of these vessels were not stained with BC05 (G). Figures C and D, E and F, and G and H are at the same magnification, respectively. Bar=100 μ m in A, B, D, F, and H.

over A β 40 in the neuritic plaques in both patients, and that A β 40 was predominant over A β 42 in cerebral amyloid angiopathy in the patient with E184D, whereas most cerebral vessels in the patient with N405S were not reactive with either of the antibodies.

ApoE genotypes of the HI-1 and the ABCD-1 cases were both ϵ 3/ ϵ 4.

Discussion

As the N405S mutation was found in a single patient without a known familial background

of dementia, we cannot exclude the possibility that this substitution corresponds to rare variants. However, the phenotype was an early onset and aggressive form of Alzheimer's disease, and the N405S substitution was not found in 100 controls and 100 patients with sporadic Alzheimer's disease. These facts may indicate that the substitution is not polymorphism and is also involved in early onset Alzheimer's disease.

The patient with the N405S mutation had numerous neuritic plaques and neurofibrillary tangles in the temporal cortex, with only occasional areas of cerebral amyloid angiopathy (fig 2). The identified risks for cerebral amyloid angiopathy are advancing age and accompanying Alzheimer's disease. Recently, the apoE ϵ 4 allele has also been associated with the presence of cerebral amyloid angiopathy and an earlier onset of haemorrhage in cerebral amyloid angiopathy.¹³ The mild cerebral amyloid angiopathy in the patient with N405S is unlikely to represent an unusually short duration of illness, an earlier age at onset, an earlier age at death, or apoE genotype, because the patient with the N405S mutation shared a similar age, duration of the disease, and one ϵ 4 allele with the patient with the E184D mutation who had abundant cerebral amyloid angiopathy.

The second feature to be noted in the patient with the N405S mutation is early manifestation of spasticity, suggesting involvement of the upper motor neurons at some level. A combination of PS1 mutant associated Alzheimer's disease and spastic paraparesis has been reported in five other pedigrees, one of which had the R278T mutation,¹⁴ and the rest were associated with the Δ 9 deletion of the PS1 gene.^{15 16} The neuropathology of the R278T mutation was not described.¹⁴ The families with the Δ 9 deletion were characterised by the occurrence of cotton wool plaques and severe cerebral amyloid angiopathy.^{15 16} These unusual features seem to be different from the pathology of the patient with the N405S mutation.

The clinical characteristics of PS1 mutant associated Alzheimer's disease cases are early manifestation of myoclonus and seizure, whereas the main pathological feature may be severe deposition of amyloid in the parenchyma and in cerebral vessels. Less cerebral amyloid angiopathy was reported in a patient with a frame shift mutation in PS1.¹⁷ Hayashi *et al*⁸ reported that PS1 antibodies stained cerebral amyloid angiopathy in Alzheimer's disease affected brains, suggesting that the PS1 protein plays a part in the formation of cerebral amyloid angiopathy. However, the extent of cerebral amyloid angiopathy is variable in PS1 mutant associated Alzheimer's disease cases, regardless of the age at onset, age at death, and duration of the disease. Variations among the patients in the amount of A β deposited as plaques seem to occur together with a variable

presence and extent of cerebral amyloid angiopathy. This is compatible with the in vitro finding that different PS1 mutations are associated with significantly different degrees of increase in A β .⁴ Previous studies indicate that the seeding peptide in plaques seems to be A β 42,¹⁹ and that the amyloid within the vessels is primarily A β 40,²⁰ which is consistent with our immunostaining results. Although it remains possible that the severity of cerebral amyloid angiopathy depends on the specific type of PS1 mutation, our data suggest that the N405S mutation is not associated with cerebral amyloid angiopathy in Alzheimer's disease.

- Sherrington R, Rogaev EI, Liang Y, *et al*. Cloning of a gene bearing missense mutations in early-onset familial Alzheimer's disease. *Nature* 1995;375:754-60.
- Scheuner D, Eckman C, Jensen M, *et al*. Secreted amyloid beta-protein similar to that in the senile plaques of Alzheimer's disease is increased in vivo by the presenilin 1 and 2 and APP mutations linked to familial Alzheimer's disease. *Nat Med* 1996;2:864-70.
- Mann DM, Iwatsubo T, Cairns NJ, *et al*. Amyloid β protein (A β) deposition in chromosome 14-linked Alzheimer's disease: predominance of A β 42(43). *Ann Neurol* 1996;40:149-56.
- Citron M, Westaway D, Xia W, *et al*. Mutant presenilins of Alzheimer's disease increase production of 42-residue amyloid beta-protein in both transfected cells and transgenic mice. *Nat Med* 1997;3:67-72.
- Borchelt DR, Thinakaran G, Eckman CB, *et al*. Familial Alzheimer's disease-linked presenilin 1 variants elevate A β 1-42/1-40 ratio in vitro and in vivo. *Neuron* 1996;17:1005-13.
- Mehta ND, Refolo LM, Eckman C, *et al*. Increased A β 42(43) from cell lines expressing presenilin 1 mutations. *Ann Neurol* 1998;43:256-8.
- Gomez-Isla T, Wasco W, Pettingell WP, *et al*. A novel presenilin-1 mutation: increased β -amyloid and neurofibrillary changes. *Ann Neurol* 1997;41:809-13.
- Yasuda M, Maeda K, Ikejiri Y, *et al*. A novel missense mutation in the presenilin-1 gene in a familial Alzheimer's disease pedigree with abundant amyloid angiopathy. *Neurosci Lett* 1997;232:29-32.
- Goelz SE, Hamilton SR, Vogelstein B. Purification of DNA from formaldehyde fixed and paraffin embedded human tissue. *Biochem Biophys Res Commun* 1985;16,130:118-26.
- Wenham PR, Price WH, Blandell G. Apolipoprotein E genotyping by one-stage PCR. *Lancet* 1991;337:1158-9.
- Iwatsubo T, Odaka A, Suzuki N, *et al*. Visualization of A β 42(43) and A β 40 in senile plaques with end-specific A β monoclonals: evidence that initially deposited species is A β 42(43). *Neuron* 1994;13:45-53.
- Schwab C, Akiyama H, McGeer EG, *et al*. Extracellular neurofibrillary tangles are immunopositive for the 40 carboxy-terminal sequence of β -amyloid protein. *J Neuropathol Exp Neurol* 1998;57:1131-7.
- Olichney JM, Hansen LA, Galasko D, *et al*. The apolipoprotein E epsilon 4 allele is associated with increased neuritic plaques and cerebral amyloid angiopathy in Alzheimer's disease and Lewy body variant. *Neurology* 1996;47:190-6.
- Kwok JB, Taddei K, Hallupp M, *et al*. Two novel (M233T and R278T) presenilin-1 mutations in early-onset Alzheimer's disease pedigrees and preliminary evidence for association of presenilin-1 mutations with a novel phenotype. *Neuroreport* 1997;8:1537-42.
- Crook R, Verkkoniemi A, Perez-Tur J, *et al*. A variant of Alzheimer's disease with spastic paraparesis and unusual plaques due to deletion of exon 9 of presenilin 1. *Nat Med* 1998;4:452-5.
- Perez-Tur J, Froelich S, Prihar G, *et al*. A mutation in Alzheimer's disease destroying a splice acceptor site in the presenilin-1 gene. *Neuroreport* 1995;7:297-301.
- Tysoe C, Whittaker J, Xuereb J, *et al*. A presenilin-1 truncating mutation is present in two cases with autopsy-confirmed early-onset Alzheimer disease. *Am J Hum Genet* 1998;62:70-6.
- Hayashi Y, Fukatsu R, Tsuzuki K, *et al*. Evidence for presenilin-1 involvement in amyloid angiopathy in the Alzheimer's disease-affected brain. *Brain Res* 1998;789:307-14.
- Jarrett JT, Berger EP, Lansbury PT Jr. The C-terminus of the beta protein is critical in amyloidogenesis. *Ann N Y Acad Sci* 1993;695:144-8.
- Alonzo NC, Hyman BT, Rebeck GW, *et al*. Progression of cerebral amyloid angiopathy: accumulation of amyloid-beta40 in affected vessels. *J Neuropathol Exp Neurol* 1998;57:353-9.