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<td>Author(s)</td>
<td>Yasuda, Minoru / Maeda, Sakan / Kawamata, Toshio / Tamaoka, Akira / Yamamoto, Yasuji / Kuroda, Shigetoshi / Maeda, Kiyoshi / Tanaka, Chikako</td>
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<tr>
<td>Citation</td>
<td>Journal of neurology, neurosurgery and psychiatry, 68(2):220-223</td>
</tr>
<tr>
<td>Issue date</td>
<td>2000</td>
</tr>
<tr>
<td>Resource Type</td>
<td>Journal Article / 学術雑誌論文</td>
</tr>
<tr>
<td>Resource Version</td>
<td>publisher</td>
</tr>
<tr>
<td>DOI</td>
<td>10.1136/jnnp.68.2.220</td>
</tr>
<tr>
<td>URL</td>
<td><a href="http://www.lib.kobe-u.ac.jp/handle_kernel/90001069">http://www.lib.kobe-u.ac.jp/handle_kernel/90001069</a></td>
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Novel presenilin-1 mutation with widespread cortical amyloid deposition but limited cerebral amyloid angiopathy

Minoru Yasuda, Sakan Maeda, Toshio Kawamata, Akira Tamaoka, Yasuji Yamamoto, Shigetoshi Kuroda, Kiyoshi Maeda, Chikako Tanaka

Abstract
Objective—To clarify the phenotypic heterogeneity in deposition of amyloid beta (Aβ) 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 Aβ42(43), resulting in an enhanced overall deposition of Aβ 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 Aβ.

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 Aβ42 was predominant over Aβ40 in neuritic plaques in both patients, whereas Aβ40 was found to be predominant over Aβ42 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 Aβ deposition but not cerebral amyloid angiopathy in Alzheimer's disease.

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 pedigree 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. Apolipoprotein E (apoE) genotyping was performed according to the method of Wenham et al. Apolipoprotein E (apoE) genotyping was performed according to the method of Wenham et al. The target PS1 gene was sequenced as described previously.

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 silver impregnation. Selected sections were also immunostained for the two types of carboxyl terminus of Aβ proteins, Aβ42(43) and Aβ40, by using end specific monoclonal antibodies. The specific affinity purified polyclonal antibodies (Quality Control Biochemicals, Inc, Hopkinton, MA, USA), β40 for Aβ C-term-40, and β42 for Aβ C-term-42, 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 of the 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, microscopic 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 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 parenchyma of this case as it was in the affected brain tissues of the ABCD-1 family with the E184D mutation.

Two Aβ40 antibodies or the two Aβ42 antibodies exhibited a similar pattern of immunostainings, respectively. Immunohistochemistry of temporal cortices from the HI-1 and the ABCD-1 cases revealed Aβ40 positive neuritic plaques containing Aβ40 peptide as in the case of the patient with sporadic Alzheimer’s disease, 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 Aβ40 (fig 2 F and H). By contrast, immunolabelling of cerebral vessels was not found either for Aβ42(43) or for Aβ40 (fig 2 C and D) in the affected brain tissues of the HI-1 case. Thus, the immunohistochemistry showed that Aβ42(43) was predominant.
over Aβ40 in the neuritic plaques in both patients, and that Aβ40 was predominant over Aβ42 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 e3/e4.

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 ε4 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 ε4 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 α9 deletion of the PS1 gene.15–16 The neuropathology of the R278T mutation was not described.14 The families with the α9 deletion were characterized 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 al18 reported that PS1 antibodies stained gyri and in cerebral vessels. Less cerebral amyloid angiopathy was reported in a patient with the N405S mutation shared a family with the patient with the N405S mutation.

11 Iwatsubo T, Odaka A, Suzuki N, et al. Visualization of Aβ42(43) and Aβ41 in senile plaques with end-specific antibody monoclonal evidence that initially deposited species is Aβ42(43). Neuron 1994;14:45–53.