Alzheimer’s disease with spastic paraparesis and ‘cotton wool’ plaques: two pedigrees with PS-1 exon 9 deletions

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Summary
Several pedigrees have recently been reported in which dominantly inherited familial Alzheimer’s disease is associated in some family members with spastic paraparesis and non-neuritic ‘cotton wool’ plaques. Here we report clinical, genetic and neuropathological findings in two further large pedigrees in which this combination of phenotypes is associated with a deletion of exon 9 of the presenilin-1 (PS-1) gene caused by mutations at the splice acceptor site. In both pedigrees, individuals with paraparesis at presentation had a later than average age at onset of symptoms. In addition, one subject with paraparesis had a much less prominent dementia syndrome than his dementia-affected siblings.

As PS-1 mutations are almost always associated with a particularly aggressive form of presenile dementia, these findings suggest the existence of a protective or delaying factor in individuals with spastic paraparesis.

Keywords: familial Alzheimer’s disease; spastic paraparesis; cotton wool plaques; presenilin-1; exon 9 splice acceptor mutation

Abbreviations: APOE = apolipoprotein E; APP = amyloid precursor protein; FAD = familial Alzheimer’s disease; MMSE = Mini-Mental State Examination; NFT = neurofibrillary tangle; PCR = polymerase chain reaction; PS-1 = presenilin-1; PS-2 = presenilin-2; RT–PCR = reverse transcription PCR

Introduction
The presenilin-1 (PS-1) gene on chromosome 14 is the most frequent gene implicated in familial Alzheimer’s disease (FAD), with over 70 mutations identified to date (listed at www.alzforum.org). The PS-1 gene product is believed to play a crucial role in amyloid precursor protein (APP) metabolism, with mutated forms resulting in increased production of the longer (42 amino acid) form of the Aβ peptide (Aβ42), which is more prone to aggregate to form fibrillar amyloid (Scheuner et al., 1996). Relating the position and in vitro effects of these causal mutations to variations in onset age, clinical and neuropathological features provide important information about the pathogenesis of Alzheimer’s disease, as well as suggesting potential avenues for prevention or treatment.

Several pedigrees have been reported in which FAD is associated with spastic paraparesis and variant neuropathology including large non-neuritic ‘cotton wool’ plaques (Crook et al., 1998). Apart from the family originally described in 1940 (van Bogaert et al., 1940), for which DNA studies have not been reported, almost all such pedigrees have been found to have a mutation in the PS-1 gene. In three of these pedigrees (Prihar et al., 1999; Hiltunen
et al., 2000; Smith et al., 2001), the genetic lesion is the deletion of several kilobases of genomic DNA, which includes the whole of exon 9 and extends into the flanking intronic sequences. We and others have reported FAD pedigrees in which the deletion of exon 9 occurs as a result of a mutation at the splice acceptor site in the PS-1 gene (Perez-Tur et al., 1995; Kwok et al., 1997; Sato et al., 1998).

In two of these pedigrees, the phenotype includes spastic paraparesis. Here we present the clinical and neuropathological features associated with the mutation in the previously reported pedigree, EOFAD-3 (Kwok et al., 1997), as well as clinical, genetic and neuropathological details of a second large pedigree, EOFAD-2, with a different splice acceptor mutation. In both these pedigrees, the variable phenotype includes spastic paraparesis and non-neuritic ‘cotton wool’ plaques.

Subjects and methods

Subjects and family ascertainment

Informed consent was obtained from the subject or next of kin for all DNA samples collected in both pedigrees, and from the next of kin for neuropathological studies. The research programme was approved by the Ethics Committee of the Central Sydney Area Health Service.

EOFAD-2

Family members are descendants of a man of Anglo-Celtic ethnicity who died at age 50 years of dementia. Little is known of his parents or siblings, but five of his six children were affected, including the proband, III:18, who died at age 60 years with Alzheimer’s disease confirmed at autopsy. Fourteen subjects in three generations have been affected, with DNA available from seven affected and four unaffected individuals. The clinical phenotype in the family was that of presenile dementia, with no confirmed instances of spastic paraparesis at the time of ascertainment. However, one subject (IV:30) who was asymptomatic at the time of blood collection has since developed spasticity and cognitive deficits. Four subjects have had autopsy confirmation.

EOFAD-3

The proband, II:6, was referred with advanced dementia at 44 years of age. She was one of 10 children. Her mother and an older sister had died with presenile dementia at 54 and 49 years, respectively. An older brother had been given a diagnosis of spastic paraparesis by a neurologist, but was not thought to be demented and lived independently at age 50 years. Two younger sisters have since developed dementia and come to autopsy. One of these developed spastic paraparesis as the dementia progressed and required a wheelchair.

Mutation screen

Genomic DNA was purified from peripheral blood leukocytes. Exons 16 and 17 of the APP gene and each coding exon of PS-1 and presenilin-2 (PS-2) were amplified by

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polymerase chain reaction (PCR) using intronic primers (Kwok et al., 1997). PCR products were screened for nucleotide substitutions by direct cycle-sequencing using Big Dye terminator chemistry fluorescent technology (Applied Biosystems, Foster City, CA, USA). Total lymphocyte RNA was isolated using the SV Total RNA Isolation System (Promega, WI, USA) and examined for PS-1 exon 9 deletion by reverse transcription-polymerase chain reaction (RT–PCR) using PS-1 primer pair ex8F11 and ex10R18 as described previously (Perez-Tur et al., 1995). Apolipoprotein E (APOE) genotypes were determined by HhaI digestion of APOE specific PCR products (Hixson and Vernier, 1990).

Neuropathology

Brains were examined with the consent of relatives, with IV:45 referred after a coronial autopsy with the consent of the next of kin. A formalin-fixed portion of upper cervical spinal cord was available from II:8 in EOFAD-3. Standard neuropathological examination was carried out. Stains included haematoxylin and eosin (H & E), myelin stains and silver stains (Bielschowsky or modified Bielschowsky). Immunohistochemistry included Tau (Sigma T5530 anti-Tau II) and Aβ (a gift from Professor Colin Masters, University of Melbourne, Australia) with peroxidase visualization. We used Congo red staining with polarized light and Aβ immunocytochemistry to detect cerebral amyloid angiopathy.

Results

In EOFAD-2, 14 members over three generations have been affected, with an age at onset ranging from 36 to 52 years (Table 1). Onset age is often not known for deceased individuals, but age at death allows some conclusions to be drawn. Individual IV:30, the only confirmed case with spasticity at presentation, developed symptoms at 48 years. Only two of the 13 other affected members (with a dementia presentation) had a later age at onset. Similarly, in EOFAD-3 (Table 1), individual II:4 developed symptoms of spasticity in his late forties and survived to age 58 years, while three of his four siblings with dementia became symptomatic in their early forties and died before 50 years. The sister (II:8) who developed spasticity survived longer, to age 51 years. The onset age of their mother, I:1, is not known, but is likely to have been before 50 years as she was aged 54 years when she died.

Case histories

EOFAD-2

III:18. This individual was admitted at age 52 years with cognitive decline over 1 to 2 years. Hospital records note lower limb weakness, particularly on the right, attributed to old polio, and associated gait disturbance with poor heel–toe manoeuvres. She also had dysarthria, which was considered unusual for Alzheimer’s disease at that stage of her illness. She died at 60 years of age. Autopsy confirmed Alzheimer’s disease (see below).

IV:30. This man was referred to a neurologist at age 48 years because of problems with walking, including stumbling and falls. Over the previous 6–12 months, he had also become forgetful (e.g. missing meetings at work), having trouble with organizational aspects of his job and having angry outbursts that were out of character. At assessment, he was vague and turned to his wife when asked questions. He had a mild slurring dysarthria. Eye movements were full and conjugate, but a little slowed. He had a spastic circumducting gait, increased muscle tone in the lower limbs with sustained ankle clonus, increased reflexes and extensor plantar responses. Upper limb tone was normal, but reflexes were exaggerated with spread to the finger flexors. Rapid alternating movements of the fingers were slowed and dysmetric. Muscle power was normal except for very mild weakness of the hip flexors. Sensory examination was normal. He is currently living at home but has stopped working.

IV:36. This secretary was referred to a neurologist at age 41 years because of deteriorating work performance, such as grossly slowed typing speed. She was forgetful but could manage her domestic responsibilities including caring for a young child. Her husband did not think she was impaired. She had difficulty giving an account of herself and made spelling errors when writing a sentence. Some months later she was admitted to hospital for assessment: she scored 20/30 on the Mini-Mental State Examination (MMSE) (Folstein et al., 1975); an MRI scan was said to show cerebral atrophy. Neurological examination was normal and, in particular, there was no spasticity or gait disorder. When seen for this study at age 45 years (by W.S.B. and G.A.B.), she was no longer working and was almost completely aphasic, but was able to walk around the town where she lived without getting lost. She could manage only minimal tasks about the house and needed some assistance with dressing and bathing. On examination, she had a pout reflex and was apraxic. Reflexes were brisk, but there was no spasticity or clonus and gait was only slightly apraxic. She had a seizure about this time and was treated with phenytoin. She lost weight and became progressively enfeebled, dying at 48 years of age. Autopsy was not performed.

IV:45. This man was admitted to a psychiatric hospital when he was 34 years old after trying to kill his wife. He was diagnosed as having morbid jealousy and was given drug treatment. He returned to his job as a miner, but continued contact with the mental health team. He separated from his wife and took redundancy from work. He was thought by some family members to have early dementia, though this was never diagnosed. He hanged himself at age 39 years; a coronial autopsy was performed (see below for neuropathology). His gait was said to be normal except for some unsteadiness when he was on medication.
II:4. This man left school at age 14 years and subsequently worked at various labouring jobs and as a truck driver. When he was 47 years, he injured his neck falling out of a truck and began to have trouble walking. His symptoms progressed and an MRI scan was performed. A neurologist diagnosed spastic paraparesis. At 51 years, he was asked to give blood for DNA studies because his mother and two sisters had developed Alzheimer’s disease. At that time, he was living alone and his family did not consider him to have dementia. He scored 23/30 on the MMSE, losing points for the date and season and for subtraction of serial sevens, though he remembered three objects after an interference task. He claimed he had not learned to write, but was able to copy intersecting pentagons. At age 54 years, he was found to have pseudobulbar palsy; by age 55 years he was in a wheelchair and had bladder problems, but was still living alone. The following year he was admitted to a nursing home, where he deteriorated over several years with slurred speech and eventually complete aphasia, intermittent confusion and agitation, worse during episodes of urinary infection and septicaemia. He was treated with norfloxacin for urinary tract infections. At age 58 years, he had several generalized seizures. He recovered, but a week later developed an infection, which did not respond to antibiotics and he was given morphine for palliation, dying within a few days. Autopsy was not performed.

II:6. This former barmaid developed memory problems at age 40 years. At neuropsychological assessment at 43 years, she could not give her address or date of birth, could not converse fluently and had difficulties with names and finding words. Writing to dictation was limited to writing her name. She had a severe amnesic syndrome and was unable to learn new information. General knowledge was deficient and she had great difficulty answering commonsense questions such as ‘why do we wash clothes?’ Visuomotor abilities were severely impaired, with marked apraxic features. She would misplace objects around the house, with plates of food left in cupboards. She believed her son was still living in the house; her husband covered all the mirrors because she thought that someone was following her. She talked to people who were not there. On neurological examination (G.A.B., W.S.B.), she had frontal release signs, positive glabellar tap and moderate rigidity of upper and lower limbs, with some cogwheeling but no spasticity. She was being treated with thioridazine at the time. Reflexes were brisk, but plantar responses were flexor. Gait was dawdling and uncertain but without ataxia or spasticity. She was cared for at home by her husband, but when he died suddenly she was admitted to a nursing home, where she survived only a few months, dying at 45 years of age. Autopsy was not performed.

II:8. This housewife developed cognitive decline in her mid-forties. When visited at 47 years for a research assessment (W.S.B.), she was clearly affected, scoring 11/30 on the MMSE, though her family had not sought medical advice at that stage. She was unable to repeat three words after six attempts; writing and drawing was limited to signing her name. On neurological examination, she had a positive
As previously reported (Kwok et al., 1997), individual II:4 from EOFAD-3 was found to carry the G→T exon 9 splice acceptor mutation in PS-1 (Fig. 2A and B). This mutation has been reported in the British family F74 (Perez-Tur et al., 1995). A G→A splice acceptor mutation was found in the proband of EOFAD-2. This mutation has been reported in the Japanese family TK-1 (Sato et al., 1998).

The results of testing 11 other members in two generations of EOFAD-2 were consistent with segregation of the G→A mutation with the disease phenotype (dementia, spastic paraparesis, or both) in an autosomal dominant manner (Fig. 1A). Individual III:22 had Parkinson’s disease with late-onset dementia when examined at the age 76 years and is considered to represent a phenocopy. RT–PCR analysis of PS-1 RNA from lymphocytes isolated from EOFAD-2 members confirmed the deletion of exon 9 sequences from PS-1 transcripts in affected individuals (Fig. 2C).

In EOFAD-3, the mutation was present in two affected siblings of II:4 but not in two unaffected siblings, a pattern consistent with segregation of the G→T mutation with the disease phenotype (Fig. 1B).

Neuropathology

**EOFAD-2**

III:18. The brain weighed 918 g and showed generalized atrophy, more prominent in the frontal and temporal lobes including the hippocampal formation. Microscopic examination revealed numerous neurofibrillary tangles (NFTs) and plaques in the hippocampus and cerebral cortex, with neuronal loss in all cortical regions. The plaques were both of the large, weakly neuritic, ‘cotton wool’ type and the classical neuritic type. Congophilic angiopathy was prominent throughout the brain. Pathology was sufficient to reach NIA–Reagan criteria for Alzheimer’s disease (National Institute on Aging and Reagan Institute Working Group on Diagnostic Criteria for the Neuropathological Assessment of Alzheimer’s Disease, 1997).

IV:23. This man died at 56 years of age in a very advanced stage of dementia. The brain weighed 910 g after fixation, although part of the left frontal lobe had been excised and frozen. There was moderate generalized atrophy. Microscopically, there was widespread plaque formation, including both large diffuse and classical neuritic plaques, throughout the cerebral cortex (Fig. 3). Marked neuronal loss and NFT formation was seen in the cerebral cortex and hippocampus, with congophilic angiopathy in parenchymal and pial vessels. Pathology was of sufficient severity to reach NIA–Reagan criteria for Alzheimer’s disease.

IV:25. The brain weighed 855 g. There was widespread atrophy, especially of the frontal lobes, with relative sparing of the temporal lobes. Bielschowsky silver stains of the cerebral cortex and hippocampus showed numerous NFTs, and many ‘cotton wool’ and classical neuritic plaques. Congophilic angiopathy was present. There was mild patchy loss of pigmented neurons of the substantia nigra with no Lewy bodies. Pathology reached NIA–Reagan criteria for Alzheimer’s disease.

IV:45. The fixed brain weighed 1550 g and showed no abnormalities on macroscopic examination. Microscopically there were very frequent large ‘cotton wool’ plaques and moderate numbers of neuritic plaques (Fig. 3). Frequent NFTs were seen in all the cortical regions examined and the hippocampus. Congophilic angiopathy was also present. This pathology satisfied NIA–Reagan criteria for Alzheimer’s disease.

**Neurology**

II:10. At 41 years, this nurse developed a gradual decline in ability with duties such as charting observations and taking telephone messages. When admitted to hospital with a pulmonary embolism, she was unable to find her room. She was seen by a neurologist, who found a mild motor apraxia and brisk reflexes but normal speech, gait and coordination; plantar responses were downgoing. On neuropsychological assessment (P.H.) 3 months later, she had marked cognitive impairment in areas including attention, visuospatial and constructional abilities, naming, recent memory and novel problem solving. She was unable to copy simple two-dimensional drawings. She had very poor concentration, being unable to recite the alphabet or count backwards from twenty. When seen at age 42 years (W.S.B.). she was quite dysphasic and unable to conduct a conversation, but could dial a few well-known numbers on the telephone, shop independently for small purchases, prepare meals and do the housework and laundry. She could walk outside the home within a block or so and did not get lost. She was independent in self-care and scored 16/30 on the MMSE. On neurological examination, she had brisk reflexes but no clonus; plantar responses were flexor and gait was normal including heel to toe walking, apart from minor unsteadiness on turning. As her dementia progressed; some years later, she developed a spastic gait and required a wheelchair. She had a seizure while still living at home. At the time of nursing home admission at age 50 years, she had very limited speech (only ‘yes’ and ‘no’). She died at 51 years (see below for neuropathology).

**Genetics**

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In EOFAD-3, the mutation was present in two affected siblings of II:4 but not in two unaffected siblings, a pattern consistent with segregation of the G→T mutation with the disease phenotype (Fig. 1B).
II:8. One hemisphere had been frozen. The fixed left hemisphere was small and the hippocampus appeared small and pale. On microscopic examination, 'cotton wool' plaques were present throughout all the neocortical regions with extremely high density (40–50 plaques per 100× field). Cored plaques were less frequent, but also present in all neocortical regions (5–10 per 100× field). NFTs, mild neuronal loss and gliosis were also present in these regions. There were very high numbers of NFTs and cotton wool plaques, but fewer cored plaques, in the hippocampus, entorhinal cortex and fusiform gyrus. Pathology was of sufficient severity to reach NIA–Reagan criteria for Alzheimer’s disease. The brainstem showed mild cell loss, but no depigmentation, gliosis or Lewy body formation in the substantia nigra and locus ceruleus. Sections of the cervical spinal cord showed degeneration of the corticospinal tracts bilaterally.

II:10. The fixed brain weighed 992 g. There was bilateral uncal herniation with necrosis of the left uncus as well as softening of the cerebellum and tonsillar herniation. On sectioning, there was significant brain swelling and the ventricles were collapsed. Recent infarction was present bilaterally in the territory of the posterior cerebral arteries and involved the cerebrum and cerebellum. The hippocampi were soft, but of normal dimensions. The cortical ribbon was of normal thickness. Sections of the cerebral cortex showed numerous (>50 per 100× field) ‘cotton wool’ plaques and smaller numbers (~10 per 100× field) of classical neuritic plaques. There were large numbers of NFTs in the temporal cortex (up to 50 per 200× field) and the hippocampal

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**EOFAD-3**

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formation and neuronal loss and gliosis were present in all cortical regions. Congophilic angiopathy was also present. Pathology was of sufficient severity to reach NIA–Reagan criteria for Alzheimer’s disease. The presence of recent infarction was confirmed in the sections from the temporal and occipital lobes, and hippocampus. The substantia nigra and locus ceruleus showed no depigmentation or inclusions. There was infarction of parts of the midbrain and pons and numerous petechial haemorrhages in the pons. The medulla oblongata and spinal cord were unremarkable.

Discussion
The two families with PS-1 exon 9 splice acceptor site mutations described in this study bring to seven the number of pedigrees now reported with exon 9 deletions (Perez-Tur et al., 1995; Kwok et al., 1997; Sato et al., 1998; Crook et al., 1998; Hiltunen et al., 2000; Smith et al., 2001); three of these pedigrees are Australian. In five of these families, the clinical phenotype as described includes spastic paraparesis. The exceptions are the British family F74 and the Finnish pedigree of Hiltunen and colleagues, in which no members have yet been reported to have paraparesis (Perez-Tur et al., 1995; Hiltunen et al., 2000; Mann et al., 2001). The neuropathological manifestations in all but the Hiltunen pedigree include non-neuritic ‘cotton wool’ plaques, although there is variability within families, and some members with a clinical phenotype of dementia have neuropathological features more usually seen in typical FAD, with significant numbers of cored plaques.

However, the concordance between spasticity, cotton wool plaques and exon 9 deletions is not complete. First, spastic paraparesis has been reported in association with other PS-1 mutations (Kwok et al., 1997; Taddei et al., 1998; Farlow et al., 2000; Houlden et al., 2000; Moretti et al., 2000; Yasuda et al., 2000; Sodeyama et al., 2001; Steiner et al., 2001; O’Riordan et al., 2002), though not with mutations in the APP or PS-2 genes. Secondly, not all reported cases with paraparesis have been found to have ‘cotton wool’ plaques. The N405S mutation was reported in a subject with neuritic plaques and only minimal congophilic angiopathy (Yasuda et al., 2000). Finally, the Finnish pedigree of Hiltunen and colleagues (Hiltunen et al., 2000) has typical early-onset Alzheimer’s disease with no spasticity or cotton wool plaques, though the family is small so far (only four affected subjects) and it is possible that a variant case may yet occur, as has happened in Aus-1 (Smith et al., 2001) and the families described here.

A further unusual feature in EOFAD3 was the occurrence of cerebral infarction causing the death of II:10 at age 45 years. Cerebral haemorrhage resulting from congophilic angiopathy is seen in conjunction with presenile Alzheimer’s disease with the APP692 mutation (Hendriks et al., 1992). Although congophilic angiopathy is a common finding in FAD, infarction or haemorrhage has not been reported in families with presenilin mutations. The APOE ε4 allele has been associated with cardiovascular disease. However, the APOE genotype of individual II:10 was ε3/ε4; her older brother had the same genotype, but did not have evidence of vascular disease.

In both these pedigrees, individuals with paraparesis at presentation had a later than average age at onset of symptoms. In EOFAD-2, the mean onset age was 44.9 years (range 36–52 years), with individual IV:30 presenting at 48 years with spasticity. Onset age is not known for his father, III:12, but his survival to age 58 years in the presence of spasticity is consistent with this hypothesis. In EOFAD-3, the mean onset age was 44.4 years (range 41–47 years), with individual II:4 developing gait problems at 47 years. In addition, this individual had a much less prominent dementia syndrome than his affected siblings. The tendency for dementia to be less prominent in individuals with spasticity...
is even more marked in our previously reported exon 9 deletion pedigree, Aus-1 (Smith et al., 2001). The diagnosis of dementia in the presence of disabling spasticity has its difficulties, since functional deficits used to diagnose dementia such as wandering, difficulty with housework or problems with dressing may be present or unassessable because of physical disability. In EOFAD-3, II:4 did not undergo neuropsychological assessment, but it was physical rather than cognitive deficits that resulted in his admission to a nursing home. In the Aus-1 pedigree, one individual has continued to maintain his performance on regular neuropsychological assessment to age 56 years without significant decline, despite severe physical disability after 12 years of spastic paraparesis.

In the pedigrees described in this paper, none of the cases coming to autopsy had paraparesis at presentation. Therefore, a full neuropathological correlation has not been possible at this stage. However, in Aus-1, we have noticed a striking difference in plaque pathology between an individual dying at 46 years with dementia only and a cousin who had both paraparesis and dementia and who died at 63 years. The dementia phenotype was associated with numerous cored plaques in the absence of variant neuropathology, whereas the individual with paraparesis had a later onset and a preponderance of ‘cotton wool’ plaques (Smith et al., 2001). Although in some pedigrees, such as Finn2, the clinical phenotype and neuropathological features appear to be fairly consistent and justify the concept of a ‘variant’ syndrome; other pedigrees, such as Aus-1 and the two families described here, include ‘variant’ cases in the context of otherwise typical FAD pedigrees.

As PS-1 mutations are almost always associated with a particularly aggressive form of presenile dementia, these findings suggest the existence of a protective or delaying factor in some individuals with paraparesis. This suggestion is based on small numbers of cases. However, continued follow-up of all available families with exon 9 deletions, spastic paraparesis, or both, should allow this issue to be examined statistically in due course as world experience accumulates. We note that, in some families with PS-1 mutations, there can be considerable variability in onset age and survival within the family, and at least one presumed ‘escape’ has been reported (Rossor et al., 1996). It seems unlikely, given the inexorable progress of neurodegeneration in most individuals with PS-1 mutations, that environmental factors are responsible for this phenotypic variability. We consider that a genetic factor is more likely. APOE genotype does not appear to play a consistent role, with ε3/ε3 and ε3/ε4 genotypes both being found in association with the paraparesis phenotype. If a dementia-protective genetic factor can be identified, this would have great potential for the development of disease-modifying or preventive therapies. These two large pedigrees may be informative for identifying such a factor.

A modifier gene may explain some perplexing findings about the effects of PS-1 mutations. For instance, the mutations associated with the paraparesis phenotype have been found to produce extremely large amounts of Aβ42 when introduced into cell culture systems (Houlden et al., 2000). These authors suggested the existence of a threshold effect, which, once exceeded, led to an alternative metabolic pathway leading to the variant neuropathology and clinical phenotype. They note, however, that the PS-1 G384A mutation causes even higher concentrations of Aβ42 than exon 9 deletions, but does not appear to be associated with spastic paraparesis (De Jonghe et al., 1999).

The variable phenotype and onset age also have implications for advising and counselling members of these and other families with PS-1 mutations. All three Australian families with PS-1 exon 9 deletions were thought at the time of ascertainment to be typical FAD pedigrees. Offspring of an affected parent in such families should not be reassured that they are no longer at risk solely because they have attained an age at which other affected members have died. The possibility that spastic paraparesis may develop in the late fifth decade should also be considered.

In summary, the clinical and neuropathological analysis of these two additional pedigrees with PS-1 exon 9 deletions reveals that the presence of spastic paraparesis and cotton wool plaques are key features associated with this class of mutation. In particular, paraparesis as a presenting feature appears to result in a delayed onset of dementia, which points to the existence of a genetic modifier locus.

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