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REVIEW

Variable phenotype of Alzheimer's disease with spastic paraparesis

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Abstract

Pedigrees with familial Alzheimer's disease (AD) show considerable phenotypic variability. Spastic paraparesis (SP), or progressive spasticity of the lower limbs is frequently hereditary and exists either as uncomplicated (paraparesis alone) or complicated (paraparesis and other neurological features) disease subtypes. In some AD families, with presenilin-1 (PSEN1) mutations, affected individuals also have SP. These PSEN1 AD pedigrees frequently have a distinctive and variant neuropathology, namely large, non-cored plaques without neuritic dystrophy called cotton wool plaques (CWP). The PSEN1 AD mutations giving rise to CWP produce unusually high levels of the amyloid β peptide (Aβ) ending at position 42 or 43, and the main component of CWP is amino-terminally truncated forms of amyloid β peptide starting after the alternative β-secretase cleavage site at position 11. This suggests a molecular basis for the formation of CWP and an association with both SP and AD. The SP phenotype in some PSEN1 AD pedigrees also appears to be associated with a delayed onset of dementia compared with affected individuals who present with dementia only, suggesting the existence of a protective factor in some individuals with SP. Variations in neuropathology and neurological symptoms in PSEN1 AD raise the prospect that modifier genes may underlie this phenotypic heterogeneity.

Keywords: Alzheimer's disease, cotton wool plaques, spastic paraparesis.

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Alzheimer's disease (AD) is one of the most common neurodegenerative diseases with a prevalence of 5–10% in individuals over 65 years. Approximately, 70% of all patients with dementia have AD (Hardy 1997). AD is characterized by cognitive impairment most notably memory loss, neuronal degeneration, amyloid plaques, cholinergic deficiency in many areas of gray matter, and the formation of abnormal cytoskeletal structures [neurofibrillary tangles (NFTs)]. The duration of AD varies widely between 5 and 15 years and the disease represents a large medical, social and economic problem.

A small percentage of patients with AD have an autosomal dominant illness that is characterized by the onset of disease at an early age (< 65 years). Most pedigrees with familial AD (FAD) have been shown to carry mutations in one of the amyloid precursor protein (APP), presenilin 1 (PSEN1) or PSEN2 genes (Hardy 1997; Price and Sisodia 1998) with over 160 PSEN1 mutations, 10 PSEN2 mutations and 28 APP mutations identified to date (see AD mutation databases http://www.alzforum.org/res/com/mut or http://www.molgen.ua.ac.be/ADMutations). The age of onset of FAD with PSEN1

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Abbreviations used: AD, Alzheimer's disease; APP, amyloid precursor protein; A*β*, amyloid beta; CWP, cotton wool plaque; FAD, familial AD; MMSE, mini mental state examination; MRI, magnetic resonance imaging; NFT, neurofibrillary tangles; PSEN1, presenilin; SP, spastic paraparesis.

mutations is the earliest observed in patients ranging from as early as the late teens to 60 years (Cruts *et al.* 1998; Moehlmann *et al.* 2002). Mutations in PSEN2 and APP appear to result in FAD with a later and more variable age of onset (40–88 years and 45–65 years, respectively) (Hutton and Hardy 1997).

Monogenic diseases typically exhibit variations in biological features, such as age of onset, severity, and multiple clinical and cellular phenotypes. Such variations can be due to specific alleles of the disease gene, environmental effects, and/or modifier genes. For example, the apolipoprotein E ε4 allele results in an earlier age of onset in FAD PSEN1 pedigrees (Pastor *et al.* 2003). Other variations in clinical features and neuropathology have been reported in families with mutations in APP and PSEN1, such as cerebral hemorrhages in association with mutations within the β amyloid coding region of APP (Levy *et al.* 1990; Van Broeckhoven *et al.* 1990). In 1997, the key observation made was that PSEN1 AD mutations were associated with the presence of spastic paraparesis (SP) suggesting that certain abnormalities in the PSEN1 protein give rise to both SP and AD (Kwok *et al.* 1997). Some individuals presenting with SP have remained dementia-free for up to 10 years (Kwok *et al.* 1997; Crook *et al.* 1998; Farlow *et al.* 2000; Smith *et al.* 2001; Assini *et al.* 2003; Brooks *et al.* 2003; Hattori *et al.* 2004). In addition, in 1998 it was shown that some PSEN1 AD pedigrees have a unique and variant neuropathology, namely large, non-cored plaques without significant neuritic dystrophy called cotton wool plaques (CWP) (Crook *et al.* 1998).

Spastic paraparesis

Spastic paraparesis is frequently hereditary and is characterized by insidiously progressive spasticity and mild weakness, predominantly in the lower limbs. SP is classified as either uncomplicated or complicated ('complex'). Uncomplicated SP has limited neurological impairment involving progressive spasticity and mild pyramidal tract weakness, often accompanied by mildly impaired vibration sensation in the distal lower extremities and hypertonic urinary bladder (Harding 1983). The primary pathology of uncomplicated SP is axonal degeneration in the distal corticospinal tracts (Schwarz and Liu 1956; Behan and Maia 1974; Harding 1993). Magnetic resonance imaging (MRI) of the brain and spinal cord are usually normal in uncomplicated SP, however, some patients have atrophy of the thoracic spinal cord (Hedera *et al.* 1999). Uncomplicated SP can begin at any age from early childhood through late adulthood. Affected individuals experience progressive difficulty in walking and often require canes, walkers, or wheelchairs. The patients typically retain normal strength and dexterity of the upper extremities and have little or late involvement of speech, chewing or swallowing. Though typically disabling, uncomplicated SP does not shorten the patient's lifespan. If the impairments present in uncomplicated SP are accompanied by other system involvement or other neurological findings, such as seizures, dementia, amyotrophy, extrapyramidal disturbances, or peripheral neuropathy, the SP is classified as complicated.

A variety of patterns of inheritance have been identified for SP consistent with the large variety of genetic influences associated with the clinical symptoms. Family history of SP is consistent with either autosomal dominant, autosomal recessive or X-linked recessive inheritance. Over 20 genetic loci have been identified for SP with mutations identified in 10 genes (Table 1) (reviewed in Fink 2003). Two dominant SP genes have been cloned to date, which together account for approximately 50% of all hereditary SP patients; spastin (SPG4) and atlastin (SPG3A). Spastin is a member of a large group of proteins known as the ATPase associated with diverse cellular activities while atlastin is a GTPase, and mutations in both genes have an average onset between 26 and 35 years. To date, two X-linked genes have been cloned, L1CAM and PLP1 which encode the neural cell adhesion molecule L1 and myelin proteolipid protein, respectively. Of particular interest are the gene loci SPG7, SPG20, ARSACS, and SPG15 responsible for four recessive forms of complicated SP for which mutations in the paraplegin (SPG7), spartin (SPG20) and sacsin genes (ARSACS) have been identified (Casari *et al.* 1998; Engert *et al.* 1999; Patel *et al.* 2002). The clinical phenotype in these families often involves dementia. No gene has been identified at the SPG15 locus but families linked to this locus frequently have dementia as the principal additional clinical feature (Hughes *et al.* 2001).

Paraplegin is a nuclear-encoded, mitochondrial protein whose primary function is not well understood. Some individuals with SPG7 gene mutations have histological (ragged red fibers) and histochemical evidence (no reaction to cytochrome *c* oxidase) of mitochondrial disturbance in skeletal muscle biopsy (Casari *et al.* 1998). The gene SPG20 encodes a protein with a microtubule interacting and trafficking molecule domain and may be involved in endosomal trafficking and/or microtubule dynamics. Mutations in the sacsin gene (ARSACS) cause a unique and characteristic feature of hypermyelinated retinal nerve fibers. Additional pathological features include atrophy of the superior cerebellar vermis, the absence of Purkinje cells, and neuronal lipid storage defects (Bouchard 1991; Bouchard *et al.* 1998). Simpson *et al.* (2003) reported a base-pair insertion in the acid-cluster protein gene 33 in an Old Order Amish family with an autosomal recessive, complicated form of hereditary SP with dementia called Mast Syndrome. The frameshift results in premature termination of the acid-cluster protein gene 33, which is designated as 'maspardin' (Simpson *et al.* 2003).

Despite the increasing understanding of the molecular basis of SP, no disease-modifying drugs are available.

Table 1 Genetic loci and genes that cause spastic paraparesis (SP)

Classification	Inheritance	Locus name	Chromosome location	Gene
Complicated SP	AD	SPG9	10q23.3–q24.1	Unknown
	AD	SPG17	11q12–q14	Unknown
	AD	SAX1	12p13	Unknown
	AR	SPG7	16q24.3	Paraplegin
	AR	SPG14	3q27–q28	Unknown
	AR	SPG15	14q22–q24	Unknown
	AR	SPG20	13q12.3	Spartin
	AR	Mast Syndrome	15q21–q22	Maspardin (acid-cluster protein)
	AR	ARSACS	13q12	Sacsin
	X-linked	SPG1	Xq28	L1CAM
	X-linked	SPG2	Xq22	PLP1
	X-linked	SPG16	Xq11.2–23	Unknown
Uncomplicated SP	AD	SPG3A	14q11–q21	Atlastin
	AD	SPG4	2p22–p21	Spastin
	AD	SPG6	15q11.1	NIPA1
	AD	SPG8	8q23–q24	Unknown
	AD	SPG10	12q13	KIF5A
	AD	SPG12	19q13	Unknown
	AD	SPG13	2q24	Hsp60
	AD	SPG19	9q33–q34	Unknown
	AR	SPG5A	8p12–q13	Unknown
	AR	SPG11	15q13–q15	Unknown
	AR	SPG21	13q14	Unknown

AD, autosomal dominant; AR, autosomal recessive.

Antispasticity drugs and regular physiotherapy remain the chief therapeutic measures in this disorder.

Alzheimer's disease, PSEN1 mutations and spastic paraparesis – clinical and neuropathological phenotypes

The occurrence of SP in a patient with AD was first reported nearly a century ago. Barrett (1913) described a patient with AD in her thirties with unusual neurological disturbances that included SP. Later, Van Bogaert *et al.* (1940) reported a Belgian kindred (family DC or CO) with FAD and SP. In three of five affected subjects, cognitive problems preceded SP, but in the two affected individuals, whose initial problem was gait difficulty, cognitive decline was not noted for 2 and 12 years, respectively. In addition to the typical plaques and NFTs of AD, both Barrett (1913) and Van Bogaert *et al.* (1940) documented generalized atrophy of the brain and degeneration of the corticospinal tracts (Barrett 1913; Van Bogaert *et al.* 1940).

In 1997, we reported the first definitive association of SP with a PSEN1 mutation, the PSEN1 R278T mutation, thereby defining a potential genetic etiology to this neurological variant of FAD (Kwok *et al.* 1997). The R278T mutation was identified in a patient who developed motor problems at 34 years and cognitive deficits at 36 years. Brain biopsy confirmed AD and the patient died aged 41 years. We also reported another FAD pedigree, SYD1, with a PSEN1 P436Q mutation, which was initially identified in an individual who developed forgetfulness in her late twenties (Taddei *et al.* 1998). At age 34, the patient had a moderate dementia, abnormal gait, and brisk reflexes with bilateral extensor plantar responses, although tone was normal. As the dementia progressed, the patient became physically more disabled with increasing spasticity, pseudobulbar palsy and rigidity, and died at 40 years (Kwok *et al.* 1997; Taddei *et al.* 1998). Since these reports, other PSEN1 mutations in AD/SP pedigrees have been reported, in particular in patients with PSEN1 exon 9 deletions. Known AD/SP pedigrees are described below and reviewed in further detail by Karlstrom *et al.* 2005 and summarized in Table 2.

Some PSEN1 mutations have also been associated with CWP neuropathology not typically observed in sporadic AD (Houlden *et al.* 2000; Smith *et al.* 2001; Steiner *et al.* 2001; Moehlmann *et al.* 2002; O'Riordan *et al.* 2002; Takao *et al.* 2002; Brooks *et al.* 2003; Kwok *et al.* 2003) (Table 2). CWP were first described by Crook *et al.* (1998) in a Finnish pedigree (FINN2). Individuals in this pedigree had both AD and SP. A 4.6-kb genomic deletion in the PSEN1 gene leading to the loss of exon 9 was identified (Crook *et al.* 1998; Prihar *et al.* 1999; Hiltunen *et al.* 2000; Verkkoniemi *et al.* 2000, 2001, 2004). Co-occurrence of the SP phenotype

Table 2 Alzheimer's disease (AD) pedigrees carrying presenilin 1 mutations that have cotton wool plaques (CWP) and spastic paraparesis (SP)

Family	PS1 mutation	Mean age of SP onset (years)	Mean age of AD onset (years)	Mean age of death (years)	Aβ 42 production[b]	Generations	Affected individuals	CWP	Clinical features	References
EB	DI83/M84	36	n.d	n.d	Increased	3	5	Yes	AD + SP	Houlden *et al.* 2000; Steiner *et al.* 2001
Japanese	L85P	27	27	n.d	Increased	–	1	n.d	AD + SP	Ataka *et al.* 2004
Japanese	Y154N	mid 30s	mid 50s	60	Decreased	2	2	n.d	AD + SP	Hattori *et al.* 2004
Michigan	InsFI ex6	30	< 30	mid 30s	n.d	4	5	Yes	AD + SP	Rogaeva *et al.* 2001; Moretti *et al.* 2004
M	G217D	–	40	48.5	n.d	2	5	Yes	AD + parkinsonism	Takao *et al.* 2002
Japanese	F237I	31	32	35	n.d	1	1	n.d	AD + SP	Sodeyama *et al.* 2001
–	V261F	38	40	–	n.d	2	4	n.d	AD + SP	Farlow *et al.* 2000
French	P264L	20–54	55	66	Increased	3	4	Yes	Atypical AD + SP	Jacquemont *et al.* 2002
Tas-1	L271V	–	49	68	Increased	3	13	Yes	AD	Kwok *et al.* 2003
P-2	R278T	34	36	41	n.d	1	1	No	AD + SP	Kwok *et al.* 1997
Italian	R278K	43	50	–	Increased	–	3	n.d	AD + SP	Assini *et al.* 2003
Irish	E280G	42	41	50	n.d	3	9	Yes	AD + SP	O'Riordan *et al.* 2002
Canadian	E280G	52	52	67	Increased	2	5	Yes	AD + SP	Rogaeva *et al.* 2003
Japanese	P284L	32	42	54	n.d	1	1	Yes	AD + SP	Tabira *et al.* 2002a
EOFAD1	Δex9 (5.9 kb)[a]	48	45	52	Increased	3	13	Yes	AD + SP	Smith *et al.* 2001
EOFAD2	Δex9 (G/A s.a)[a]	48	44	48	Increased	3	14	Yes	AD + SP	Kwok *et al.* 1997
EOFAD3	Δex9 (G/T s.a)[a]	44	45	50	Increased	2	6	Yes	AD + SP	Brooks *et al.* 2003
FINN2	Δex9 (4.6 kb)[a]	50	52	55	Increased	4	23	Yes	AD + SP	Crook *et al.* 1998
FINN3	Δex9 (4.6 kb)[a]	–	43.5	n.d	Increased	2	4	Yes	AD	Hiltunen *et al.* 2000
TK-1	Δex9 (G/A s.a)[a]	47	47	62.5	Increased	4	12	Yes	AD + SP	Sato *et al.* 1998; Mann *et al.* 2001; Tabira *et al.* 2002a
F74	Δex9 (G/T s.a)[a]	42	–	54	Increased	3	7	Yes	Dyskinesia + SP	Perez-Tur *et al.* 1995; Mann *et al.* 2001
TOR	Δex9[a]	n.d	n.d	n.d	n.d	4	14	Yes	AD + SP	Rogaeva (personal comm.)
Japanese	N405S	50s	48	53	Increased	1	1	Yes	AD + SP	Yasuda *et al.* 2000
SYD-1	P436Q	34	< 30	40	Increased	1	1	?	AD + SP	Taddei *et al.* 1998
D	P436Q	29	n.d	n.d	Increased	2	3	Yes	AD + SP	Houlden *et al.* 2000
UK	P436Q	35	42.5	49	Increased	2	2	Yes	AD + SP	Beck *et al.* 2004
CO/DC	n.d	31	38	n.d	n.d	3	5	Yes	AD + SP	Van Bogaert *et al.* 1940; Houlden *et al.* 2000
Japanese	n.d	28	31	36	n.d	1	1	Yes	AD + SP	Tabira *et al.* 2002a
Japanese	n.d	26	27	37	n.d	1	1	Yes	AD + SP	Tabira *et al.* 2002a
Japanese	n.d	28	30	36	Increased	1	1	Yes	AD + SP	Yokota *et al.* 2003
Japanese	n.d	–	39	46	Aβ40 increased	1	1	Yes	AD	Yokota *et al.* 2003
Japanese	n.d	–	34	45	Increased	1	1	Yes	Parkinson's + dementia	Yokota *et al.* 2003

s.a, splice acceptor site; n.d, not defined.

[a]Sometimes called Δexon 10 because of untranslated exon identified in the 5′ end of the gene.

[b]Aβ 42 production is measured either in cell lines or in primary cultures.

with AD delayed the onset of dementia symptoms by 5 years. Neuropathology showed degeneration of the lateral corticospinal tracts and a profusion of CWP concentrating in the frontal motor cortices. Memory impairment was present in all patients appearing either simultaneously with or preceding walking difficulties because of SP. The variation in this pedigree, such as the occurrence of SP and the delayed onset of dementia, suggests the involvement of a factor protective against dementia. Hiltunen *et al.* (2000) reported another Finnish family FINN3, which has the same genomic deletion as the FINN2 family but without SP or CWP, and instead has the clinical and neuropathological phenotype, typical of AD (Hiltunen *et al.* 2000).

CWP are easily discernable by their large size (over 100 μm in diameter), ability to stain with eosin (Fig. 1a), lack of a central amyloid core (Fig. 1d), sparse glial response (Fig. 1g) and neuritic infiltrate (Fig. 1b). They have sharply demarcated margins and an appearance of displacement of surrounding tissue (Tabira *et al.* 2002a). When immunostained, CWP exhibit intense Aβ42 immunoreactivity and weak or no Aβ40 immunoreactivity (Mann *et al.* 2001; Takao *et al.* 2002; Shepherd *et al.* 2004; Ishikawa *et al.* 2005). They are only weakly fluorescent when stained with thioflavin S, indicating very little fibrillar Aβ (Takao *et al.* 2002). Tau deposition in CWP is also of the non-fibrillar type. Non-hyperphosphorylated tau has been demonstrated in and around CWP with tau-2 immunostaining (Shepherd *et al.* 2004) while antibody PHF-1 immunostaining shows little reactivity (Mann *et al.* 2001). These characteristics are in contrast to those of classic or diffuse deposits seen in sporadic AD (Fig. 1). Classic senile plaques which are usually ca. 50 μm in diameter, have a central Aβ protein core (Fig. 1e) and surrounded by dystrophic neurites (Fig. 1c) which may contain ubiquitin or paired helical filaments on immunostaining. Activated microglia and astrocytes are often observed within these plaques (Fig. 1h). Diffuse plaques are deposits of Aβ protein that are less dense and more irregular in shape than classic senile plaques and have no central core (Fig. 1f). Like CWP, they are non-neuritic and are accompanied by little inflammatory response

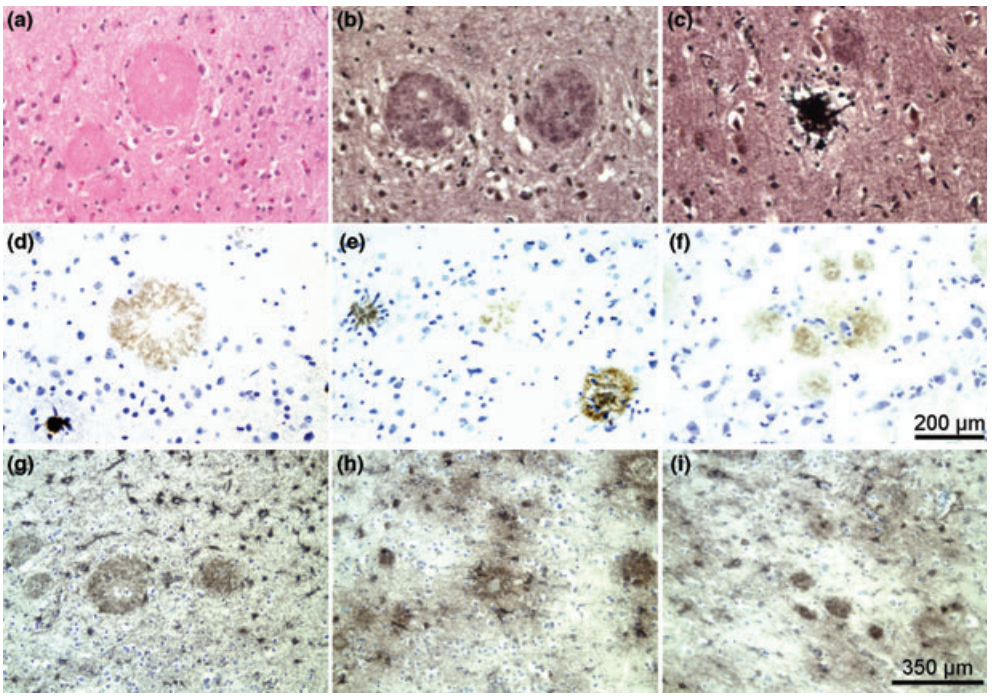

Fig. 1 Photomicrographs of cotton wool (a, b, d and g), classic (c, e and h) and diffuse (f and i) plaques in a patient with a presenilin 1 mutation and Alzheimer's disease (AD; a–d) and a patient with sporadic AD (c, e, f, h and i). Scale in f is equivalent for a–f. Scale in i is equivalent for g–i. (a) Hematoxylin and eosin staining shows large, well-marginated acellular cotton wool plaques (CWP) in the upper layers of the cortex. (b) Modified Bielschowsky silver stain shows that CWP are large non-cored cortical depositions without neuritic infiltrates. (c) Modified Bielschowsky silver stain shows dense neuritic infiltrates in classic-cored plaques. (d) Aβ40 immunohistochemistry with cresyl violet counter-staining shows that cotton wool plaques are poorly stained without a concentrated core. (e) Classic plaques are intensely immunoreactive for Aβ40 with a concentrated core. (f) Diffuse deposits can also be seen following Aβ40 immunohistochemistry with cresyl violet counter-staining. (g) Glial fibrillary acidic protein (GFAP) immunohistochemistry with cresyl violet counter-staining shows a fine meshwork of asrocytic processes, although the CWP do not contain enlarged glial cells. (h) GFAP immunohistochemistry with cresyl violet counter-staining shows that classic plaques have a clear acellular core surrounded by up-regulated glial cells. (i) GFAP immunohistochemistry with cresyl violet counter-staining shows dense astrocytic processes but no up-regulated glial cells in diffuse plaques.

(Fig. 1i), however, they do not display distinct margins or disrupt structures of the surrounding neuropil (Adlard and Vickers 2002; Morgan *et al.* 2004). The paucity of inflammatory mediators, such as the complement components C1q, C3d, and C9, in CWP (Crook *et al.* 1998) suggests an alternative pathway for their induction and ongoing maintenance compared with the typical neuritic plaques which are accompanied by high levels of inflammation in the brain (Probst *et al.* 1991). Indeed, functional studies show that the PSEN1 mutations and deletions associated with CWP produce unusually high levels of Aβ42 and that these peptides often are amino-terminally truncated, starting at the glutamate residue 11 (Table 2; Miravelle *et al.* 2005). There are some sporadic late-onset AD patients without PSEN1 mutations that have been reported to have CWP, consistent with the concept that CWP arise from excessive Aβ1–42 production (Fukatsu *et al.* 1980; Le *et al.* 2001; Yokota *et al.* 2003).

Houlden *et al.* (2000) reported three families with AD and SP which share the characteristic CWP pathology; the Scottish family EB had a deletion of two nucleotides and consequently two amino acids in PSEN1 exon 4 (DelI83/M84), the Belgian family CO, which was first described by Van Bogaert *et al.* (1940) as family DC with no identified PSEN1 mutation and the British family D, with the PSEN1 P436Q mutation and CWP (Taddei *et al.* 1998; Houlden *et al.* 2000). The Scottish family was studied in more detail by Steiner *et al.* (2001) who demonstrated that this deletion caused the typical increase in Aβ1–42 levels and reduced activity in Notch signaling found in other PSEN1 mutations causing CWP (Steiner *et al.* 2001). A Canadian family, the large TOR pedigree with a PSEN1 exon 9 deletion has a large sibship, comprising six affected individuals with variable occurrence of AD and SP also suggesting an involvement of a modifier gene (Dr E Rogaeva, personal communication). Farlow *et al.* (2000) reported a PSEN1 V261F mutation in a patient who developed leg stiffening at age 38, but no memory impairment. Some years later, he developed dementia and was wheelchair bound. A similar syndrome was reported in the proband's father, sister, and paternal aunt (Farlow *et al.* 2000). In most of these families, wherein SP was a prominent clinical feature, the characteristic pathology of CWP has also been confirmed.

Mann *et al.* (2001) described a British family, F74 [also described by Perez-Tur *et al.* (1995)], and a Japanese family, TK1, both of which have a splice acceptor mutation causing a deletion of PSEN1 exon 9 and FAD. A consequence of the loss of PSEN1 exon 9 is that the truncated transcript also carries an additional amino acid substitution, S290C, arising from the codon spanning the splice site. The F74 proband was said to be dyskinetic and have CWP in the frontal cortex. Tabira *et al.* (2002a) described identical twins from the TK1 family where one developed memory disturbances followed by SP and the other reported trembling and neuralgic pain of the left lower leg with an earlier onset of memory impairment. Both brothers had numerous neuritic and CWP in hippocampus, frontal, temporal, and parietal cortices (Tabira *et al.* 2002a).

Ten different Japanese pedigrees have been reported with both AD and AD with SP, five of which have a mutation in PSEN1 (F237I, N405S, P284L (one pedigree each) and deletion of exon 9 (two pedigrees) and five pedigrees have no reported mutations. All patients had numerous CWP and NFTs (Yasuda *et al.* 2000; Sodeyama *et al.* 2001; Tabira *et al.* 2002a; Yokota *et al.* 2003). The patient with F237I developed SP at the age of 31 years, mild memory impairment – 1 year later and died at 35 years. A positron emission tomography scan demonstrated marked, bilateral hypometabolism and hypoperfusion in the temporoparietal areas as well as in the somatomotor cortices (Sodeyama *et al.* 2001). Takao *et al.* (2002) reported another Japanese family 'M' with five affected subjects from two generations who have CWP but not SP. Two siblings had a clinical phenotype characterized by dementia and parkinsonism with stooped posture, rigidity and bradykinesia. Numerous CWP, senile plaques and NFTs were identified in both patients. Genetic analysis revealed a G217D PSEN1 mutation (Takao *et al.* 2002).

Jacquemont *et al.* (2002) reported a small French family with a PSEN1 P264L mutation wherein individuals had dementia described as not typical of AD and preceding SP. The proband presented at 54 years with gait problems and lower back pain; at 55 years, the proband had SP and dementia, scoring 18/30 on the Mini mental state examination (MMSE), but the authors considered the pattern of cognitive deficits not typical of AD. Brain MRI showed mild atrophy. There was a family history of dementia in his sister (died aged 63), mother (died aged 70) and maternal grandmother (age at death unknown). Walking difficulties were noted in his mother (Jacquemont *et al.* 2002). Ataka *et al.* (2004) have recently published a case report of a Japanese man with a PSEN1 L85P missense mutation which was not present in either parent or two siblings. The man developed AD and SP at the age of 27 with a predominant visuospatial cognitive deficit (Ataka *et al.* 2004).

An Irish family with a PSEN1 mutation E280G has individuals with either AD or both AD and SP (O'Riordan *et al.* 2002). One sibling had AD, internuclear ophthalmoplegia, spastic-ataxic quadriparesis, with CWP and amyloid angiopathy on brain biopsy. Another sibling had AD, SP and white matter abnormalities on MRI, while a third sibling had similar MRI abnormalities and AD, but without SP. The authors considered that the MRI findings may reflect an ischemic leukoencephalopathy because of amyloid angiopathy affecting meningocortical vessels (O'Riordan *et al.* 2002) as has been suggested in individuals with the Dutch APP693 mutation, where pre-symptomatic carriers have white matter changes on MRI (Bornebroek *et al.* 1996). We

have also seen severe white matter change in a member of the EOFAD1 pedigree with both SP and AD (Smith *et al.* 2001).

Brooks *et al.* (2003) described two FAD kindreds where SP was present in some members. The EOFAD2 family has a deletion of exon 9, this time because of the G/A splice acceptor mutation, first reported in a Japanese family by Sato *et al.* (1998). Affected individuals had FAD onset symptom at an age ranging from the late thirties to the early fifties. Four affected members had typical AD without SP, one with a relatively late onset age of 48 years, developed SP concurrently with cognitive impairment. The EOFAD3 family carry the exon 9 G/T splice acceptor mutation first described in British family F74 by Perez-Tur *et al.* (1995). Most individuals had cognitive impairment as a presenting feature in their early forties and died in their late forties or early fifties, but one mutation-positive individual presented in his late forties with spasticity, surviving until 58 years. A sibling who presented with dementia developed spasticity subsequently and died at 51 years. Neuropathological examination of the cervical spinal cord showed bilateral degeneration of the corticospinal tracts (Brooks *et al.* 2003).

Smith *et al.* (2001) reported an Australian early-onset kindred, EOFAD1, which has a 5.9-kb genomic deletion over exon 9. Members of two generations developed presenile AD, confirmed by autopsy in two patients. Members of one sibship in the third generation, at 50% risk, remained asymptomatic for AD until their mid-forties, an age at which affected family members usually had established cognitive decline, although four siblings subsequently developed SP. One died of breast cancer without apparent dementia. At autopsy, there was pyramidal tract degeneration in the medulla and spinal cord with pyramidal cell loss in the motor cortex and significant numbers of CWP but very few NFTs and no significant neuron loss elsewhere in the brain. Another sibling became cognitively impaired in her fifties at about the same time as she developed SP and at autopsy had pyramidal tract degeneration and AD with CWP together with cerebral amyloid angiopathy. Brain MRI had previously shown severe white matter disease, though this was not found in her brother, who had only mild dementia at the time of admission to an institution at 59 years because of disabling spasticity in the lower limbs and subsequent bulbar involvement with impaired speech and swallowing. In this family, it is notable that the mean age of onset of symptoms in individuals with SP at presentation is later than that for individuals with a dementia at presentation. For individuals with SP at presentation, either alone or with cognitive decline, cortical CWP were a feature, compared to subjects with only dementia who developed the characteristic neuritic AD plaques. This suggests that CWP are associated with SP, either with or without AD. Again, the involvement of a protective factor or modifier gene seems to be the most likely explanation for the phenotypic variations within this pedigree (Smith *et al.* 2001).

Other reports are consistent with this hypothesis. Assini *et al.* (2003) reported an Italian family of three affected individuals with a PSEN1 R278K mutation. One member had dementia with onset at 48 years, one had SP with onset at 45 years followed by dementia 5 years later, and one man had SP with onset at 41 years and only a focal memory deficit after 12 years (MMSE score of 28/30) (Assini *et al.* 2003). Rogaeva *et al.* (2003) reported a Canadian family of five affected subjects in two generations. The pedigree has an E280G PSEN1 mutation, previously reported by O'Riordan *et al.* (2002) although erroneously published as an E280Q mutation (Dr E. Rogaeva, personal communication). The proband had memory difficulties and weakness in both legs beginning at 52 years (duration of 15 years). Neuropathology showed degeneration of the corticospinal tracts (Rogaeva *et al.* 2003). Hattori *et al.* (2004) reported a PSEN1 Y154N mutation in which the proband had gait disturbances beginning at 37 years and memory difficulties at 42 years. On admission at an age of 47, the proband had SP and an MMSE of 16/30. The proband's mother also presented with gait disturbance in her forties and died at 69 years after 2 years of abnormal behavior and cognitive dysfunction, however, she remained non-demented for at least 10 years after the onset of gait disturbance (Hattori *et al.* 2004).

Kwok *et al.* (2003) described a Tasmanian family Tas-1, with a PSEN1 missense mutation L271V resulting in a PSEN1 transcript isoform that lacks exon 8. The isoform lacking exon 8 increases the secretion of Aβ1–42 without interacting with either the tau or glycogen synthase kinase-3β proteins, providing an explanation for the lack of dystrophic neurites in the CWP found in this family. The Tas-1 family has clinical features consistent with AD without SP but with CWP neuropathology, indicating that CWP may occur without the SP phenotype (Kwok *et al.* 2003).

Moretti *et al.* (2004) described a Michigan family with a heterozygous 6-nucleotide insertion (TTATAT) at nucleotide position 715 of the PSEN1 gene, PSEN1 InsFI located in exon 5. This mutation has also been described by Rogaeva *et al.* (2001) and causes an unusually aggressive form of AD that maintains the usual regional hierarchy of pathology while extending abnormalities into more widespread brain areas than typically seen in sporadic AD. The proband had dementia beginning at 28 years. By 32 years, he had dystonic dysarthria, limb dystonia and SP with spontaneous clonus. A positron emission tomography scan initially showed hypometabolism in the posterior temporoparietal cortex but a later scan showed more severe changes which encompassed the posterior cingulate, primary motor and frontal association cortices. The involvement of the primary motor cortex was apparent only after SP was clinically noticeable. Both his father and paternal grandfather were affected and died at 42 years and 35 years, respectively (Rogaeva *et al.* 2001; Moretti *et al.* 2004).

Beck *et al.* (2004) reported a family from UK where germline and somatic mosaicism of the PSEN1 P436Q mutation was found in a woman who died at 58 years after a 16-year history of progressive parkinsonism, mild SP and dementia. The mutation was not found in DNA from peripheral blood. Neither parent nor siblings were affected but her daughter carried the P436Q mutation and developed a progressive cerebellar syndrome at 27 years with SP and dementia, and died after 12 years (Beck *et al.* 2004).

Overall there are 165 different PSEN1 mutations (in 361 pedigrees) described to date, of which 17 (in 24 pedigrees) can lead to SP, although all lead to AD. These mutations are relatively evenly spaced along the gene ; 7% found in exon 13 and 21% found in exons 5 and 7, respectively. The stark exception is exon 9, which has only 1.4% of PSEN1 mutations leading to AD, but has an enrichment of cases with an AD/SP phenotype (5–6% of AD/SP vs. 1–2% with mutations not affecting exon 9) (Karlstrom *et al.* 2005). Thus, mutations affecting exon 9 are markedly over-represented in FAD patients with SP, suggesting again that specific PSEN1 FAD mutations, together with a modifying factor, may explain this phenotypic variation.

Mechanisms of cotton wool plaque formation

The biochemical relationship between CWP and clinical phenotype could not adequately be explained by extracellular Aβ deposition, as there are patients who have clear CWP pathology without any clinical signs (Yokota *et al.* 2003). There are, however, increasing lines of evidence that intracellular Aβ molecules, probably in the oligomeric or protofibrillar forms are neurotoxic (Chui *et al.* 2001; Steiner *et al.* 2001). Intraneuronal Aβ has been reported to be present more frequently in AD patients with CWP than with neuritic plaques (Tabira *et al.* 2002b; Takao *et al.* 2002). Furthermore, it has been shown that CWP are mainly composed of amino-terminally truncated forms of Aβ, indicating that the generation and deposition of Aβ peptide of different lengths may represent the basis for the morphology of Aβ deposits. These may be because of tissue-specific factors or arise because γ-secretase with certain PSEN1 FAD mutations favors the β-secretase-cleaved fragment starting at glutamate-11 (the C89 fragment) instead of aspartate-1 (the C99 fragment), generating the Aβ11–42/43 fragment (Miravelle *et al.* 2005).

Houlden *et al.* (2000) have offered the suggestion of an increased amount of Aβ1–42 or a dosage effect for the pathogenesis of the SP variant. Transfection experiments reveal that the most SP-causing mutations selectively increase Aβ1–42 production compared with those mutations that lead to the more typical dementia phenotype (Houlden *et al.* 2000) (Table 2). Dumanchin *et al.* (2006) have also determined the biological effects of four PSEN1 FAD mutations causing AD with SP and CWP and found a significant increase in Aβ42/40 ratio in three of four mutations. However, it was observed that increased Aβ42 levels provide a complete explanation of the CWP/SP phenotype (Dumanchin *et al.* 2006). Over-expression of 14 different PSEN1 FAD mutations, together with the C99 substrate in COS-7 cells, also led to an increase in the Aβ42/Aβ40 ratio (Duering *et al.* 2005).

While these proposals may explain the presence of CWP in AD/SP pedigrees, they do not provide an explanation for the altered sites of neuropathology such as the degeneration of the motor cortex, which is normally spared in AD, and the degeneration of the corticospinal tracts. However, intracellular Aβ could be an important factor as there is evidence for extracellular CWP morphology without any clinical signs (Crook *et al.* 1998; Yokota *et al.* 2003).

Mechanisms causing intra-familial variation in phenotypes

Many different PSEN1 mutations are associated with classic FAD. However, a striking variation in clinical presentation occurs in some AD pedigrees in which some individuals have SP, either preceding, concurrent with, or instead of dementia and with brain pathology characterized by Aβ-positive CWP (Table 2 and Fig. 1). The dementia phenotype is unusual as dementia onset appears in some pedigrees to be delayed compared with the affected individuals who present with dementia only. The phenotypic variability could be because of environmental effects, specific alleles of the PSEN1 gene, the involvement of modifier genes or a combination of the two latter alternatives. However, the variable presentation of SP and dementia within large sibships carrying identical PSEN1 mutations, who presumably have many common environmental exposures, suggests that both environmental factors and specific PSEN1 alleles may not be the primary determinant of AD/SP.

Several forms of complicated SP are associated with dementia and we have reviewed above many pedigrees with PSEN1 mutations that also have SP. An obvious experimental approach to understand the cause of this variable phenotype is to analyze the common SP genes by mutation screening (Table 1). Mutations in three SP genes, spastin, atlastin and paraplegin, account for approximately 50% of all hereditary SP patients. However, no coding sequence variation has been observed in these genes in several AD/SP pedigrees (Rogaeva *et al.* 2003; Karlstrom *et al.* 2007). Mutation screening of the coding exons and flanking introns of a further six SP genes in Australian FAD/SP pedigrees has also been undertaken without detecting any sequence variations (Karlstrom *et al.* 2007). A second group of genes which might be implicated in the AD/SP phenotype are those involved in the phosphorylation of the tau protein. These are strong candidates for the

CWP phenotype as one of the main differences between demented patients with and without SP is the lack of neuritic involvement surrounding the plaques in patients with SP. Thirdly, candidate genes involved in Aβ degradation may also be involved in disease pathogenesis and the production of CWP. There are however, no reports examining the potential role of these genes to date. Other ways by which modifier genes might be identified include the use of cDNA microarray analysis of brain tissues from individuals with or without SP or linkage analysis on a cohort of pedigrees with AD/SP to determine if there is a genetic (modifier) locus that is co-inherited with the SP phenotype. These may be fruitful areas of future research.

The exact mechanism by which the AD/SP phenotype arises remains to be determined. Moreover, some individuals in AD pedigrees with SP have a delayed onset of dementia despite the deposition of Aβ in CWP, perhaps by a mechanism that prevents pyramidal cell loss in non-motor cortical regions Thus, the identification of the biological mechanisms that give rise to the variable phenotype is of potential significance for the design of novel therapeutics based on obviating the pathogenic effects of Aβ.

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