Alzheimer's disease, the most common cause of dementia in later life, is genetically heterogeneous. Mutations in three genes encoding the amyloid precursor protein (APP), presenilin 1 (PSEN1), and presenilin 2 (PSEN2) are responsible for autosomal dominant early onset cases. A few families have been described in which PSEN1 mutations, usually exon 9 deletions, cause progressive dementia associated with spastic paraparesis.1–3 We present a family in which another PSEN1 mutation causes disease that begins with spastic paraparesis and is associated with dementia that is not of the Alzheimer type.

The index case first presented at the age of 54 with lower back pain and gait difficulties; he was unable to squat unaided and walked with caution. He complained of a memory deficit that he attributed to the Algerian war, 34 years ago. On examination, he had brisk reflexes in all four limbs and normal muscle tone. Blood cell counts, CSF glucose and protein levels, electromyography, and nerve conduction velocity were unremarkable. A lumbar CT scan and cervicothoracic MRI showed no signs of spinal compression. Brain MRI showed mild cortical atrophy.

One year later, the patient had a bilateral extensor plantar reflex, with clonus of the patella and proximal muscle weakness in the lower limbs. There was no sign of cerebellar ataxia, and sensory modalities of the trunk and limbs were not affected. A second brain MRI showed mild cortico-subcortical atrophy. He was referred to our clinic at the age of 55 with the diagnosis of spastic paraparesis. He could not walk for more than one mile and complained of frequent falls. Gait was markedly spastic, but muscle tone at rest was normal. In addition to the pyramidal syndrome, there was gait evoked nystagmus, saccadic ocular pursuit, and marked orthostatic hypotension. Dementia was evident, with a Mini Mental Status Examination (MMSE) score of 18/30 with deficits in visuospatial abilities and long term memory deficits (with respect of recognition) in the absence of other mnemonic, instrumental, or executive dysfunctions. Deletions of exon 9 in the PSEN1 gene have been found in three pedigrees. The R278T, P436Q, and del IM at position 83-84 mutations have been detected in one family each. In vitro, exon 9 deletions increase the AB 42/AB 40 ratio. Surprisingly, the P264L mutation found in our family has been described in several families with Alzheimer's disease, but never in association with spastic paraplegia.1–4 Interestingly, dementia in our patient was not typical of Alzheimer's disease, since the cognitive impairment was less severe, as expected according to the young age and long disease duration. There was only impairment of visuospatial abilities and long term memory deficits (with respect of recognition) in the absence of other mnemonic, instrumental, or executive dysfunctions. Deletions of exon 9 in the PSEN1 gene have been found in three pedigrees. The R278T, P436Q, and del IM at position 83-84 mutations have been detected in one family each. In vitro, exon 9 deletions increase the AB 42/AB 40 ratio. Surprisingly, the P264L mutation found in our family has been described in several families with Alzheimer's disease, but never in association with spastic paraplegia.1–4 It seems unlikely, however, that this association resulted from random association in four family members. Alternatively, two gene defects, the P264L PSEN1 mutation and another mutation responsible for spastic paraplegia, might segregate in the family. However, the SPG3 locus for autosomal dominant spastic paraparesis also located on chromosome 14 is not genetically linked to the PSEN1 gene and is associated with an early onset
(2 to 15 years), in contrast to this family. Our results strongly suggest that the association of dementia and spastic paraparesis is not restricted to specific PSEN1 mutations, but may also represent variable phenotypic expression of more common mutations usually causing typical Alzheimer's disease. It is interesting that the P264L mutation can result in dementia that is not typical of Alzheimer's disease.

Authors' affiliations
M-L Jacquemont, A Brice, A Durr, Département de Génétique Médicale, Cytogénétique et Embryologie, Hôpital de la Salpêtrière, Paris, France
D Campion, T Frebourg, INSERM EPI 9906, Faculté de Médecine et de Pharmacie, Institut Fédératif de Recherches Multidisciplinaires sur les Peptides, Rouen, France
V Hahn, C Tallaksen, A Brice, A Durr, Département de Neurologie, Hôpital de la Salpêtrière, Paris, France
C Tallaksen, A Brice, A Durr, INSERM U289, Hôpital de la Salpêtrière, Paris, France

Correspondence to: Dr A Durr, Département de Génétique Médicale, Cytogénétique et Embryologie, Hôpital de la Salpêtrière, Paris, France; durr@ccr.jussieu.fr

REFERENCES