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ARTICLE

Mental deficiency in three families with *SPG4* spastic paraplegia

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Mutations and deletions in the *SPG4* gene are responsible for up to 40% of autosomal dominant hereditary spastic paraplegia (HSP). Patients have pyramidal signs in the lower limbs and some present additional features including cognitive impairment such as executive dysfunction or subcortical dementia. We report 13 patients from three *SPG4* families, who had spastic paraplegia associated with mental retardation ($n=1$), extensive social dependence ($n=10$), or isolated psychomotor delay ($n=2$). In family FSP-698, 10 affected individuals had both HSP and mental deficiency leading to social dependence in 9 and institutionalization in 5. The mean age at onset of spastic paraplegia was 11 ± 20 years, ranging from 1 to 51 years. This phenotype segregated either with a novel p.Glu442Lys mutation or the two previously described p.Arg459Thr and p.Arg499Cys substitutions in the *SPG4* gene. Since two of these mutations were previously reported in families with a pure form of the disease, another genetic factor linked to *SPG4* could be responsible for this complex phenotype.
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Introduction

Hereditary spastic paraplegias (HSP) are clinically characterized by the presence of gait spasticity, muscle weakness and increased reflexes in the lower limbs (LL). Many patients may also have sphincter disturbances and decreased vibration sense at ankles.[1–4] This phenotype defines clinically pure HSP, whereas complicated forms are associated with other neurological signs such as peripheral neuropathy, mental retardation (MR), impairment of executive functions or dementia, cerebellar atrophy, optic atrophy or non-neurological signs such as gastrooesophageal reflux.

HSP may be transmitted as autosomal dominant (AD), autosomal recessive (AR) or X-linked (XL) diseases. Autosomal dominant transmission accounts for 70–80% of all HSP.[5–7] Among the nine genes (*SPG3A*, *SPG4*, *SPG6*, *SPG8*, *SPG10*, *SPG13*, *SPG17*, *SPG31*, *SPG33*) and four loci (SPG9, SPG12, SPG19, SPG29) responsible for AD-HSP, *SPG4* accounts for 15–40% of the families.[1,8–10] *SPG4* encodes a 616-amino acid named spastin, which belongs to the AAA family (ATPases associated with diverse cellular activities). The AAA domain of spastin is located in the C terminus of the protein between amino acids 342 and 599. Emerging evidence suggests that spastin plays a role in microtubule dynamics[11] and that mutations in the spastin gene could lead to alteration of intracellular organelles trafficking.[12] All type of *SPG4* mutations have been

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described, including missense, nonsense, splice-site mutations, small insertions and deletions[9] as well as large exonic deletions,[13,14] which strongly suggests that the pathogenic mechanism of *SPG4* mutations is haploinsufficiency (ie, disease occurs once the level of functional spastin falls below a critical level). So far, genotype–phenotype studies have not revealed a clear correlation between mutation types and age at onset or disease severity.[9,15,16] The intragenic polymorphisms S44L and P45Q are, however, associated with earlier age at onset.[17–19]

SPG4 mutations and deletions most often result in pure HSP with a mean age at onset of 29 ± 17 years, ranging from infancy to 76 years.[1,9,14] However, complicated forms associated to variable degrees of cognitive decline, MR, epilepsy or cerebellar ataxia in addition to spasticity were described.[20–28] We previously showed that carriers of *SPG4* mutation had subtle executive dysfunctions, which were absent in noncarriers relatives.[28] Mental retardation was reported in *SPG4* patients with cerebral malformations such as dysplasia of the corpus callosum[27] or congenital arachnoid cyst.[22] We describe 13 patients from three *SPG4* families, who have spastic paraplegia associated with mental deficiency without cerebral malformation.

Patients and methods

Patients

During diagnostic screening for *SPG4* mutations in 543 families with available clinical information, we identified three families in whom MR, mental deficiency or psychomotor delay was associated with spastic paraplegia and *SPG4* mutations. The probands were seen at the outpatients clinic of the Department of Genetics and Cytogenetics, Salpêtrière Hospital in Paris. Their relatives who could not come to the hospital were examined by one of us at their home or in their institutions. Families FSP-698 and FSP-748 originated from different regions of France, whereas family AAR-392 originated from Morocco. Informed consent was obtained from each family member before blood sampling.

Methods

Clinical assessment Age and sign at onset were noted for each patient, according to the patient and relatives. Gait spasticity was measured with a four-point scale, with 0 = none, 1 = mild, 2 = moderate and 3 = severe. Functional impairment was assessed with a seven-points scale (0 = none, 1 = no functional impairment but signs at examination, 2 = mild, 3 = moderate, 4 = walking with one cane, 5 = walking with two canes and 6 = wheelchair-bounded). Psychomotor delay was assessed when patients acquired sitting position after the age of 9 months, gait after the age of 18 months or comprehensible speech after the normal delay of 18–24 months. Social dependence was assessed when patients needed help for daily-life activities, such as finance management, self-direction, social skills, home living, and so on. Mental retardation was defined by the DSM IV criteria, as having an IQ < 70, onset before the age of 18 years and at least two of the following: limitation in self-care, home living, social skills, community use, self-direction, health and safety, functional academics, leisure and work.[29] IQ testing could be done in patients AAR-392-II-1 and FSP-698-II-3 who could attend a medical centre. We could not obtain IQ testing or neuropsychological examinations in the other patients, who were examined at home or in their institutions. Previous IQ tests and neuropsychological examinations were collected for patients FSP-698-II-4 and III-2, including global cognitive efficiency testing (WAIS III, MATTIS and MMS tests), memory test (Grober and Buschke), executive tests (FAB, Wisconsin card sorting test), language, praxic and visuo-spatial abilities testing. Cognitive deterioration was distinguished from MR by a worsening progression.

For patients who could not attend our consultation, we collected results of available additional investigations such as cerebral magnetic resonance imaging (MRI), neuropsychological examination or electromyography (EMG). In the proband of families without autosomal dominant transmission, we performed a metabolic screening including serum amino-acid chromatography, urine organic acids chromatography, very long-chain fatty acids dosage and measurement of lysosomal enzymes activities. Search for FMR1 CGG repeat amplification, responsible for fragile X syndrome was performed in patients FSP-748-III-2 and FSP-698-II-3 and high-resolution karyotype in the three index patients.

Analysis of the SPG4 gene The 17 coding exons of the *SPG4* gene were screened by denaturing high-performance liquid chromatography (DHPLC) in the three probands, as already described.[30] Samples showing abnormal elution profiles were re-amplified from genomic DNA. Forward and reverse sequence reactions were performed with the Big Dye Terminator Cycle Sequencing Ready Reaction Kit using the same primers (PE Applied Biosystems). The sequence products were analysed on an ABI 3730 automated sequencer (PE Applied Biosystems). Three hundred European and one hundred North African controls (mostly healthy spouses of patients with neurological diseases) were tested to rule out polymorphisms in the spastin gene.

To test for a common haplotype in families with the p.Arg499Cys mutation, we selected five microsatellite markers (D2S352, D2S2203, D2S2351, D2S2325 and D2S2347) flanking the SPG4 locus. We also developed four additional intragenic *SPG4* microsatellite markers, located in intron 2 (ATT10), intron 3 (TAT17), intron 4 (TAG14) and intron 9 (TG15), respectively. Finally, six SNP located in the 3′-UTR of the gene (rs7572964, rs4952252, rs4952207, rs4519572, rs4407291 and rs4530415) were genotyped. Template DNA was denatured at 94°C for

5 min, followed by 35 cycles of amplification at 94°C 30 s, 55°C 30 s and 72°C 30 s, then by a final step of elongation at 72°C for 7 min. PCR products were mixed with deionized formamide and the GENESCANTM 400HD ROX standard (Applied Biosystems) and denatured at 95°C for 5 min, before analysis on an ABI 3730 automated sequencer (Applied Biosystems). Genotypes were analysed with GeneMapper 3.5 software (Applied Biosystems).

Results

Clinical features

Pedigrees of the three families are shown in Figure 1. Transmission of spastic paraplegia was dominant in families FSP-698 and FSP-748. In family AAR-392, the proband was an isolated case. The mean age at examination was 40.5 ± 13.1 years, ranging from 22 to 63 years (Tables 1a and b). The mean age at onset of spasticity was 11.0 ± 19.7 years, ranging from 1 to 51 years. Six patients could not remember the age when they started having difficulties in walking, but noted that it was during childhood ($n=3$), adolescence ($n=1$) or as long as they could remember ($n=2$).

Gait spasticity was severe in eight patients, moderate in three and mild in two. Functional motor impairment varied from none to severe, with four patients using a wheelchair. All patients presented increased reflexes in the LL, 77% (10/13) in upper limbs (UL). Plantar reflexes were extensor in all symptomatic patients. Vibration sense at ankles was decreased in nine patients. Seven patients suffered from sphincter disturbances.

Cerebral MRI performed in five patients was normal ($n=2$), showed cortical and subcortical atrophy ($n=3$) (Figure 2) or white matter abnormalities ($n=1$). Medullar atrophy was present in the four patients who had medullar MRI.

Cognitive features in family FSP-698

Patient III-2 fitted with all the DSM IV criteria of MR. MR was also diagnosed in patients II-1, II-2 and II-4 who had psychomotor delay in childhood, were institutionalized and totally dependent at the time of examination.

Patients II-3, III-3 and IV-1 had psychomotor delay and were dependent for daily-life activities. Patient II-3 did not have mental retardation since his IQ was within the

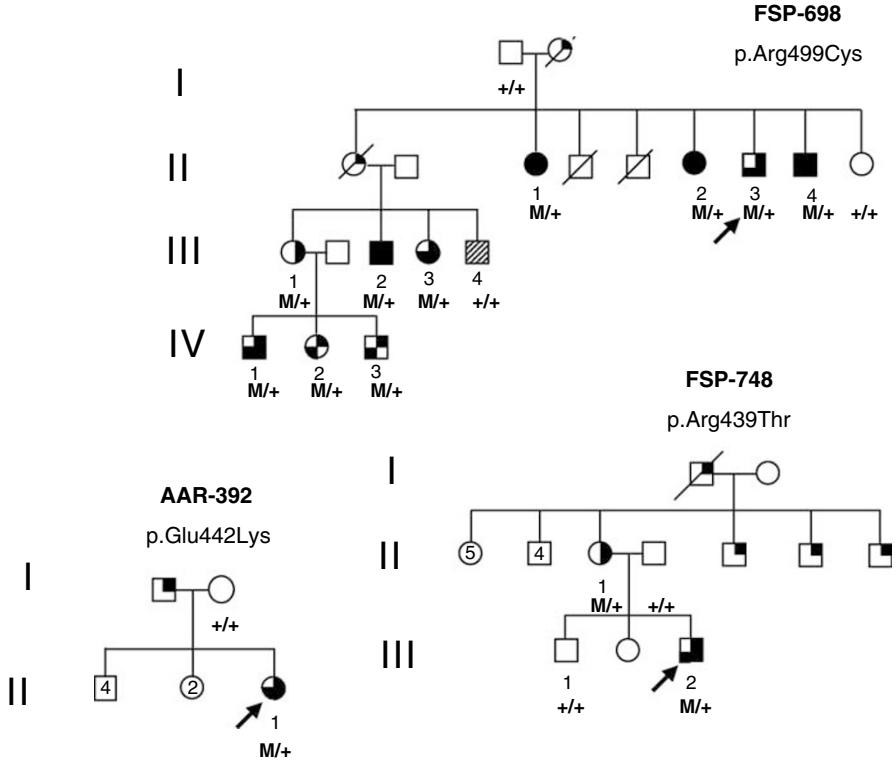

Figure 1 Pedigrees of three families with HSP and mental difficulties. *Upper right black corner*: spastic paraplegia. *Lower right black corner*: psychomotor delay (sitting position acquired after the age of 9 months, gait after the age of 18 months or comprehensible speech after 18–24 months of age). *Upper left black corner:* mental retardation. *Lower left black corner*: social dependence (help needed for daily-life activities, such as monthly finance management, self-direction, social skills, home living, etc). *Hatched symbol*: patient with psychotic disorder and autistic features, without pyramidal signs at examination. *Numbers under the symbols*: sampled and examined patient's numbers according to generations I–IV. The SPG4 mutations are indicated under the family identification number. M/+: heterozygote mutation, +/+: homozygous wild-type alleles.

Table 1a Clinical features of 10 patients of family FSP-698

Patient number	*II-1*	*II-2*	*II-3*[a]	*II-4*	*III-1*	*III-2*	*III-3*	*IV-1*	*IV-2*	*IV-3*
Age at examination (years)	63	55	53	47	45	43	39	29	27	24
Age at onset (years)	Childhood	51	Adolescence	4	5	Birth	Childhood	Birth	1	Childhood
Sign at onset	Stiff legs	Stiff legs	Stiff legs	Stiff legs	Stiff legs	Never acquired gait	Tip toes gait	Stiff legs	Stiff legs	Stiff legs
Neurological impairment										
Gait spasticity	3	1	3	3	3	3	3	3	2	2
Functional impairment	6	2	5	6	5	6	6	3	3	2
Increased reflexes (LL)	+	+	+	+	+	+	+	+	+	+
Increased reflexes (UL)	+	+	+	+	+	−	+	+	−	−
Extensor plantar reflexes	Bilateral	Bilateral	Bilateral	Bilateral	Bilateral	Bilateral	Bilateral	Bilateral	Bilateral	Bilateral
Vibration sense alteration at ankles	+	+	+	+	+	+	+	−	+	−
Sphincter disturbances	+	+	+	+	+	+	−	−	+	−
Psychomotor delay	+	+	+	+	+	+	+	+	−	−
Cognitive impairment										
Intellectual deterioration	−	+	−	+	−	−	−	−	−	−
Institutionalized	+	+	+	+	−	+	−	−	−	+
Help needed for daily life	Totally	Totally	Partially	Totally	None	Totally	Partially	Partially	Partially	Totally
Additional investigations										
Neuropsychological examination	ND	ND	IQ:100	Homogenous impairment of all intellectual functions	ND	IQ:70	ND	ND	ND	ND
Cerebral MRI	ND	ND	Cortical and subcortical atrophy, nonspecific WMH	Cortical atrophy	ND	Cortical and subcortical atrophy	ND	Normal	ND	ND
Medullar MRI	ND	Medullar atrophy	Medullar atrophy	Medullar atrophy	ND	Medullar atrophy	ND	ND	ND	ND

IQ = Intellectual quotient, ND = not done, WMH = white matter hypersignals, + = yes, − = no. Functional impairment: 0 = none, 1 = no functional impairment but signs at examination, 2 = mild, 3 = moderate, 4 = walking with one cane, 5 = walking with two canes and 6 = wheelchair-bounded. Gait spasticity: 0 = none, 1 = mild, 2 = moderate and 3 = severe.
[a]Index patient.

Table 1b Clinical features of three patients of families AAR-392 and FSP-748

Family-patient	*AAR-392-II-1*[a]	*FSP-748-II-1*	*FSP-748-III-2*[a]
Age at examination (years)	30	49	22
Age at onset (years)	1	No complain	4
Sign at onset	Stiff legs		Stiff legs
Neurological impairment			
Gait spasticity	3	0	2
Functional impairment	4	1	3
Increased reflexes (LL)	+	+	+
Increased reflexes (UL)	+	+	+
Extensor plantar reflexes	Bilateral	No	Unilateral
Vibration sense alteration	−	+	−
Sphincter disturbances	−	−	−
Psychomotor delay	+	+	+
Cognitive impairment			
Intellectual deterioration	−	−	−
Institutionalized	−	−	−
Help needed for daily life	Partially	None	Partially
Additional investigations			
Neuropsychological examination	IQ:91	ND	ND
Cerebral MRI	ND	ND	Normal

ND = not done, + = yes, − = no. Functional impairment: 0 = none, 1 = no functional impairment but signs at examination, 2 = mild, 3 = moderate, 4 = walking with 1 cane, 5 = walking with 2 canes and 6 = wheelchair-bounded. Gait spasticity: 0 = none, 1 = mild, 2 = moderate and 3 = severe.
[a]Index patient.

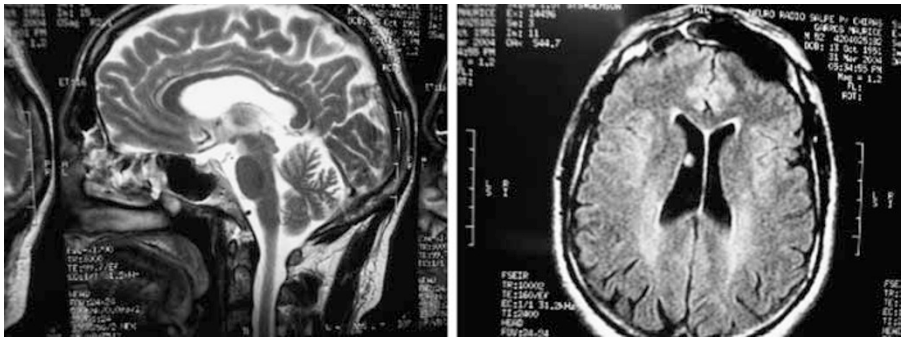

Figure 2 Cerebral MRI of patient FSP-698-II-3 at age 53 years. Sagittal and coronal cerebral pictures, showing global cortical and subcortical atrophy, as well as periventricular white matter abnormalities.

normal range (100), but he was partially dependent for daily-life activities. He lived in an institution.

Patients IV-2 and 3 were noninstitutionalized, without history of psychomotor delay, but were socially dependent.

Patient FSP-698-III-1 had isolated psychomotor delay, was not institutionalized and did not have IQ testing. Her mental status remained uncertain.

Patient III-4, unaffected for HSP, was institutionalized in a psychiatric hospital since the age of 10 years, with a diagnosis of severe psychotic disorder with autistic features. He had no language and was not tested for IQ. We considered his mental status as undetermined.

Mental deficiency was not progressive in all but two patients (FSP-698-II-2 and FSP-698-II-4), who complained about memory deterioration, since the age of 50 and 44 years, respectively.

Cognitive features in family FSP-748

Patient II-1 had increased reflexes in LL, vibration sense alteration and psychomotor delay. She was not institutionalized and did not have IQ testing. Her mental status remained uncertain.

Patient III-2 had psychomotor delay and was dependent for daily-life activities.

Cognitive features in family AAR-392

Patient II-1 had psychomotor delay and was dependent for daily-life activities. As for patient FSP-698-II-3, she had no

mental retardation (IQ = 91), but mental deficiency was suggested by her social dependence. Cognitive impairment was confirmed by neuropsychological examination which showed low performances at MMS (27/30) and particularly MATTIS (126/144) tests. In addition, impairment of executive functions such as attention and verbal fluency (14/18 at the FAB) was evident. Cognitive impairment and affective immaturity were also suggested by learning difficulties as soon as in primary school, associated to introverted behavioural abnormalities. She worked in a centre for mentally disabled persons.

Her mother had a normal neurological examination at age 58 years. Her 62 years old father was reported to have cognitive and gait difficulties, but did not allow to be examined.

Molecular results

An abnormal DHPLC profile was observed in exon 13 of the proband of family FSP-698, caused by a C>T substitution at position 1495 of the coding sequence. This change, which causes the p.Arg499Cys substitution, is a recurrent mutation previously described in other families with HSP.[9,30–32] In family FSP-748, an abnormal profile in exon 11 revealed the presence of the c.1376G>C/p.Arg459Thr missense mutation, which has been previously reported in another HSP family.[33] A novel missense mutation in exon 11, c.1324G>A/p.Glu442Lys, was identified in the proband of family AAR-392. Glutamic acid at position 442 is located in the AAA cassette of spastin and is conserved in mammals as well as in *Drosophila* and *Fugu*. This novel mutation was not found in a large control population of 800 chromosomes. Neither the S44L nor P45Q *SPG4* intragenic polymorphisms have been found in the probands of the three families.

SPG4 mutations segregated both with HSP and mental deficiency in families FSP-698 and 748. In family FSP-698, a bi-point LOD score of 3.0102 was calculated when the mental status of patients FSP-698-III-1 and 4 was considered as undetermined. The former had isolated psychomotor delay associated with HSP and the latter had autistic features without HSP. This result suggests that the p.Arg499Cys mutation in family FSP-698 is associated with a mental deficiency of variable severity, ranged from psychomotor delay to mental retardation.

The p.Arg499Cys mutation was also identified in two other families who had HSP without mental impairment (Depienne *et al*, in preparation). To determine whether the mutation in these two families occurred independently from that of family FSP-698 or came from a common ancestor, we genotyped seven microsatellite markers, four of which were located inside the *SPG4* gene and six SNP in the patients of the three families. The results were consistent with a possible common ancestor for the two families with pure HSP, but revealed that the mutation occurred independently in family FSP-698 (Table 2).

Table 2 Haplotyping results of three families with the p.Arg499Cys mutation, including two with a pure spastic paraplegia and family FSP-698 with spastic paraplegia and mental retardation

								SPG4 gene							
			Intron 2	*Intron 3*	*Intron 4*	*Intron 9*	*Exon 13*		*Intron 15*			*3′-UTR*			
Location															
Marker	*D2S2203*	*D2S2351*	*ATT10*	*TAT17*	*TAG14*	*TG15*	*c.1495C>T*	*rs7572964*	*rs4952252*	*rs4952207*	*rs4519572*	*rs4407291*	*rs4530415*	*D2S2325*	
Proband 638-7	262	236/237	154	252/264	297/309	174	T	A	C	T	A	G	T	187	
Family 618	262	236	154	252	297	174	T	A	C	T	A	G	T	187	
Family 698	262	241	157	250	297	174	T	A	T	C	G	A	C	187	

Discussion

We report 13 patients from three families with MR, mental deficiency or psychomotor delay associated to *SPG4*-related HSP. This is the first study that reports mental retardation or deficiency in patients with *SPG4* mutations and without cerebral malformation.

Neuropsychological examination or IQ testing could be obtained for four patients only, since the others were institutionalized or could not attend a medical centre. One patient (FSP-698-III-2) fitted the DSM IV criteria for MR, three others (FSP-698-II-1, 2 and 4) were institutionalized, totally dependent and had psychomotor delay in childhood. Two patients (FSP-698-IV-2 and 3) without psychomotor delay were socially dependent in daily life, suggesting mental deficiency. The remaining seven patients had psychomotor delay in early childhood, five of whom (FSP-698-II-3, III-3, IV-1, FSP-748-III-2 and AAR-392-II-1) were also dependent of relatives in daily life, suggesting the presence of intellectual difficulties and social inadaptation. Patients AAR-392-II-1 and FSP-698-II-3 had an IQ slightly inferior to average, ranging from 91 to 100. Nevertheless, we used the term of 'mental deficiency' because of the extensive social dependence associated with executive dysfunction, affective immaturity, behavioural and social inadaptation.

Cognitive impairment was reported by us and others in patients with *SPG4* mutations.[20,21,23,24,26,28,34] Compared to the early onset in childhood leading to social dependence in adulthood observed in our patients, it was usually mild without functional impairment and limited to executive dysfunction, although it could occasionally progress to subcortical dementia. Cognitive decline may be present before the onset of spastic paraplegia.[20,21,24] Mental deficiency in our patients was clearly distinct from cognitive deterioration, as it was evident since infancy and was not progressive.

Common causes of MR were excluded by metabolic screening in the proband of family AAR-392, chromosomal analyses in the three index patients and PCR analysis of the FMR1 repeat segment in two male patients (FSP-748-III-2 and FSP-698-II-3). In addition, X-linked mental retardation not related to HSP was unlikely because of the similar disease severity in male and female patients.

Mental retardation was already described in patients with *SPG4* mutations, but they all had in addition cerebral malformations such as dysplasia of the corpus callosum[27] or congenital arachnoid cyst.[22] No malformation or other structural abnormality was found in five of our patients.

Our patients had slightly different HSP clinical characteristics compared to the previously described *SPG4* patients without mental impairment. Age at onset of spasticity was earlier in our patients (11 ± 19.7 *versus* 29 ± 17 years),[9,35] who also presented more frequently brisk reflexes in UL (77%), compared to 20–30% in *SPG4* patients without MR.[2,9] However, the proportion of patients who had increased UL reflexes increased with disease duration,[9] which was longer in our patients compared to *SPG4* patients without MR (29.2 ± 13.4 *versus* 21 ± 15 years).

Although the p.Glu442Lys mutation found in family AAR-392 is novel, the p.Arg499Cys and p.Arg459Thr mutations were previously described in families with pure HSP and in an isolated patient with spastic paraplegia associated to dementia.[9,30–33] This suggests that the *SPG4* mutations in our patients are not sufficient to explain the presence of mental deficiency or psychomotor delay, but that other genetic factors could explain the phenotype. The S44L or P45Q *SPG4* intragenic polymorphisms were absent in the probands of the three families. They have not been described with complicated HSP forms, but account for pure HSP forms with early age at onset.

For the LOD score calculation, two patients were considered with an undetermined clinical status for mental deficiency: (1) patient FSP-698-III-4 who did not carry the *SPG4* mutation nor had spastic paraplegia. He had a psychotic disorder with autistic traits and lived in a psychiatric institution since the age of 10 years. He had no language and could not be tested for IQ to assess whether or not he was mentally retarded. (2) Patient FSP-698-III-1 had HSP and psychomotor delay in childhood. She was able to live alone without assistance, and was not tested for IQ. The LOD score reached 3.0102 in family FSP-698, suggesting a nonrandom association between HSP, SPG4 and mental deficiency of variable severity, ranging from psychomotor delay to mental retardation.

Segregation of HSP with mental deficiency in family FSP-698 argues in favour of a variant linked to *SPG4*, that is, located in the chromosome 2 interval shared by all the affected individuals. This hypothesis is in agreement with the finding that the p.Arg499Cys mutation in family FSP-698 occurred independently than the same mutation found in two other families with pure HSP. However, we cannot exclude that a micro-rearrangement on chromosome 2 or on another chromosome could also segregate in the 10 patients of family FSP-698 and account for the presence of mental deficiency in this family.

These findings extend the clinical spectrum of the *SPG4*-associated phenotypes, which should be tested in patients with spastic paraplegia even with mental retardation or psychomotor delay. Additional genetic studies need to be carried out to identify all genetic factors responsible for this complicated phenotype.

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