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Mutations in *SPG11* are frequent in autosomal recessive spastic paraplegia with thin *corpus callosum*, cognitive decline and lower motor neuron degeneration

Giovanni Stevanin,[1,2,3,*] Hamid Azzedine,[1,2,4,*] Paola Denora,[1,2,5,*] Amir Boukhris,[1,2,3,6] Meriem Tazir,[7] Alexander Lossos,[8] Alberto Luis Rosa,[9] Israela Lerer,[10] Abdelmadjid Hamri,[11] Paulo Alegria,[12] José Loureiro,[13] Masayoshi Tada,[14] Didier Hannequin,[15,16] Mathieu Anheim,[17] Cyril Goizet,[1,2,18] Victoria Gonzalez-Martinez,[19] Isabelle Le Ber,[1,2] Sylvie Forlani,[1,2] Kiyoshi Iwabuchi,[20] Vardiela Meiner,[10] Goekhan Uyanik,[21] Anne Kjersti Erichsen,[22] Imed Feki,[6] Florence Pasquier,[23] Soreya Belarbi,[7] Vitor T. Cruz,[13] Christel Depienne,[1,2,3] Jeremy Truchetto,[1,2] Guillaume Garrigues,[19] Chantal Tallaksen,[22] Christine Tranchant,[17] Masatoyo Nishizawa,[14] José Vale,[12] Paula Coutinho,[13] Filippo M. Santorelli,[5] Chokri Mhiri,[6] Alexis Brice,[1,2,3] Alexandra Durr[1,2,3] and on behalf of the SPATAX consortium[†]

[1]INSERM, U679, [2]Université Pierre et Marie Curie - Paris 6, UMR S679, [3]APHP, Département de Génétique et Cytogénétique, Groupe Hospitalier Pitié-Salpêtrière, Paris, [4]Centre de Référence de Neurogénétique, CHU d'Angers, France, [5]Unit of Molecular Medicine, IRCCS-Bambino Gesù Children's Hospital, Rome, Italy; [6]Service de Neurologie, Hôpital Habib Bourguiba, Sfax, Tunisia, [7]Service de Neurologie, Hôpital Mustapha, Algiers, Algeria, [8]Department of Neurology, Hadassah-Hebrew University Medical Center, Jerusalem, Israel, [9]Laboratorio de Biologia Cellular y Molecular, Fundacion Allende and Sanatorio Allende, Cordoba, Argentina, [10]Department of Human Genetics, Hadassah-Hebrew University Medical Center, Jerusalem, Israel, [11]Hôpital Benbadis, Constantine, Algeria [12]Serviço Neurologia, Hospital De Egas Moniz, Lisboa, [13]Departamento de Neurologia, Hospital S. Sebastiao, Santa Maria da Feira, Portugal, [14]Department of Neurology, Brain Research Institute, Niigata University, Niigata, Japan, [15]Department of Neurology, Rouen University Hospital and [16]INSERM, U614, Rouen, France, [17]Neurology Department, Hôpital Civil, Strasbourg, France, [18]Service de Génétique, Hôpital Pellegrin, Bordeaux, France, [19]Service de Neurologie, CHU de Montpellier, Hôpital Gui de Chauliac, Montpellier, France, [20]Neurological Clinic of Yokohama, Yamate, Japan, [21]Department of Neurology, University of Regensburg, Germany, [22]Ulleval University Hospital, Oslo, Norway and [23]Centre Hospitalier Régional Universitaire, EA2691, Lille, France

[*]The first three authors contributed equally to this work.
[†]The members of the SPATAX consortium are listed in the Appendix.

Correspondence to: Prof Alexis Brice, INSERM U679, IFR de Neurosciences, Pitié-Salpêtrière Group, 47 Bd de l'Hôpital, 75013 Paris, France
E-mail: brice@ccr.jussieu.fr

Hereditary spastic paraplegias (HSP) are neurodegenerative diseases mainly characterized by lower limb spasticity associated, in complicated forms, with additional neurological signs. We have analysed a large series of index patients ($n = 76$) with this condition, either from families with an autosomal recessive inheritance ($n = 43$) or isolated patients ($n = 33$), for mutations in the recently identified *SPG11* gene. We found 22 truncating mutations, including the first four splice-site mutations, segregating in seven isolated cases and 13 families. Nineteen mutations were novel. Two recurrent mutations were found in Portuguese and North-African patients indicating founder effects in these populations. The mutation frequency varied according to the phenotype, from 41%, in HSP patients presenting with a thin *corpus callosum* (TCC) visualized by MRI, to 4.5%, in patients with mental impairment without a TCC. Disease onset occurred during the first to the third decade mainly by problems with gait and/or mental retardation. After a mean disease duration of 14.9 ± 6.6 years, the phenotype of 38 SPG11 patients was severe with 53% of patients wheelchair bound or bedridden. In addition to mental retardation, 80% of the patients showed cognitive decline with executive dysfunction. Interestingly, the phenotype also frequently included lower motor neuron degeneration (81%) with wasting (53%). Slight ocular cerebellar signs were also noted in patients with long disease durations. In addition to a TCC (95%), brain MRI revealed white matter

alterations (69%) and cortical atrophy (81%), which worsened with disease duration. In conclusion, our study reveals the high frequency of *SPG11* mutations in patients with HSP, a TCC and cognitive impairment, including in isolated patients, and extends the associated phenotype.

Keywords: spastic paraplegias; SPG11; thin corpus callosum; mental retardation; lower motor neuron degeneration

Abbreviations: AR = autosomal recessive; HSP = hereditary spastic paraplegias; IQ = intellectual quotient; LL = lower limbs; MMSE = Mini Mental State Evaluation; UL = upper limbs; SPG = spastic paraplegia gene; TCC = thin corpus callosum; WMA = white matter abnormalities

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Introduction

Hereditary spastic paraplegias (HSP) are neurodegenerative conditions in which the main clinical features are progressive spasticity and weakness of the lower limbs associated with posterior column or bladder involvement (Harding, 1983; Filla *et al.*, 1992; Tallaksen *et al.*, 2001). This phenotype can be complicated by the presence of a wide range of additional neurological and non-neurological signs or symptoms including mental retardation, deafness, cerebellar ataxia, epilepsy, dysarthria, ichthyosis, optic atrophy, peripheral neuropathy, retinitis pigmentosa, cataract, etc. These diseases are inherited in an autosomal dominant, autosomal recessive (AR) or X-linked manner and a wide genetic heterogeneity has been demonstrated with the identification of more than 33 loci and 15 genes (Fink, 2006; Mannan *et al.*, 2006; Valdmanis *et al.*, 2007; Stevanin *et al.*, 2007). The most common forms of autosomal dominant HSP, accounting for about 50% of patients, are caused by mutations in the *SPG4* and *SPG3A* genes that encode for spastin and atlastin, respectively (Hazan *et al.*, 1999; Zhao *et al.*, 2001).

In AR-HSP, observed more frequently than autosomal dominant HSP in inbred populations (Coutinho *et al.*, 1999), the first three genes identified that encode paraplegin (*SPG7*), spartin (*SPG20*) and maspardin (*SPG21*) (Casari *et al.*, 1998; Patel *et al.*, 2002; Simpson *et al.*, 2003), as well as the gene responsible for the related spastic ataxia of Charlevoix Saguenay (Engert *et al.*, 2000), represent only a small proportion of all cases (Fink, 2003). Strikingly, about one-third of AR-HSP index patients have a thin or atrophied *corpus callosum* (ARHSP-TCC) visualized by MRI with different degrees of cognitive deficit (Franca *et al.*, 2007). This form of AR-HSP was initially mapped to chromosome 15q13-15 [*SPG11*, (Martinez *et al.*, 1999)] and accounts for 41–77% of reported ARHSP-TCC families (Shibasaki *et al.*, 2000; Casali *et al.*, 2004; Stevanin *et al.*, 2006). Recently, the *SPG11* gene, also known as *KIAA1840/FLJ21439*, that encodes spatacsin, was identified and was mutated in 11 of 12 ARHSP-TCC index patients (Stevanin *et al.*, 2007). Ten different mutations were identified in the 11 families. They were either nonsense mutations, deletions or insertions in the *SPG11* coding sequence, resulting theoretically in an abnormally truncated protein in all cases.

The aims of the present study were to estimate the frequency of *SPG11* mutations in a large series of patients with ARHSP with or without TCC, mental retardation or cognitive impairment, to define the spectrum of the mutations in this gene and to describe the associated phenotypes.

Materials and Methods

Subjects

Forty-three kindreds with an autosomal recessive inheritance and 33 isolated cases with no family history of the disease were selected, 22 and 5 of which were consanguineous, respectively. Index patients presented with either (i) spastic paraplegia with a mental retardation or cognitive impairment and TCC visualized at MRI ($n = 26$), (ii) spastic paraplegia with TCC without mental retardation and cognitive impairment ($n = 11$) or (iii) spastic paraplegia with mental retardation or cognitive impairment without TCC ($n = 22$). In addition, 17 index patients presenting with spastic paraplegia and mental retardation or cognitive impairment for which MRI was not available were also analysed. This study has been approved by the local Bioethics committee (approval no 03-12-07 of the Comité Consultatif pour la Protection des Personnes et la Recherche Biomédicale Paris-Necker to Drs A. Durr and A. Brice). Informed written consent has been given by all participating members of the families before blood samples were collected for DNA extraction. All clinical evaluations were performed according to a protocol established by the European and Mediterranean network for spinocerebellar degenerations (SPATAX, coordinator: Dr A. Durr) that included: full medical history and examination, estimation of the age at onset by the patient, presence or absence of additional neurological symptoms/signs, electroneuromyographic (ENMG) studies and brain MRI when possible. IQ or Mini Mental State Evaluations (MMSE) (Folstein *et al.*, 1975) were available for 12 patients, two of whom had detailed neuropsychological evaluations including Standard Progressive Matrices [PM38, (Raven, 1982)] and the Wechsler Memory Scale (Wechsler, 1987). According to the DSM-IV criteria (Diagnosis and statistical Manual of Mental disorders, 2000), mental retardation was considered when the patient had an IQ < 70 before the age of 18 years.

Most patients were French ($n = 37$) or North-African ($n = 15$), or originated from other European countries ($n = 13$), the Middle-East ($n = 6$) and elsewhere ($n = 5$). Eleven of the 33 sporadic subjects previously tested negative for mutations or

rearrangements in the *SPG4* gene (Depienne *et al.*, 2006, 2007); mutations in the *SPG7* gene were also excluded in a subset ($n = 20/43$) of families (Elleuch *et al.*, 2006).

Genotyping

Linkage to *SPG11* was investigated in 33 AR-HSP families using the polymorphic markers *D15S781, D15S537, D15S516* and *D15S659* after DNA amplification by polymerase chain reaction (PCR); the amplicons were sized on an ABI Prism 3730 automated sequencer with GenMapper software (Applied Biosystems, Foster City, CA, USA), as previously described (Stevanin *et al.*, 2006). After haplotype reconstruction, putative linkage was established on the basis of common haplotypes by descent in affected relatives of the same pedigree.

Mutation detection

The coding sequence and splice site boundaries of the 40 exons of the *SPG11* gene were amplified by PCR and sequenced in both directions as described previously (Stevanin *et al.*, 2007).

Numbering of new mutations/polymorphisms was performed relative to the ATG codon of the first coding exon, as recommended by the Human Genome Variation Society (http://www.hgvs.org/mutnomen/). Segregation of the mutations/polymorphisms with the disease was verified by direct sequencing in 64 additional family members whose DNA samples were available. In addition, unrelated healthy subjects were screened to evaluate the frequency of nucleotidic changes: 80 French Caucasians, 31 North-Africans, 103 Palestinians and 48 individuals from Argentina. Synonymous, missense and splice-site variations were systematically evaluated for modifications of exonic splicing enhancers (ESEfinder algorithm available at http://www.rulai.cshl.edu/cgi-bin/tools/ESE/esefinder.cgi) or consensus splicing sequences (at http://rulai.cshl.edu/new_alt_exon_db2/HTML/score.html and http://www.fruitfly.org/seq_tools/splice.html). Multiple alignment with spatacsin orthologs in various species was performed using ClustalW software (http://www.ebi.ac.uk/clustalw/) to evaluate conservation of missense variants.

The effect on mRNA splicing of a variant affecting the last codon of exon 15 was analysed by RT-PCR on RNA extracted from the lymphoblasts of patient FSP670-5, as reported elsewhere (Stevanin *et al.*, 2007) using primers cDNAF—GCT CTGTGGTGGGATCAACT (exon 14) and cDNAR—TGCTTA CACTGGCCTGATTG (exon 18) at an annealing temperature of 60°C, followed by direct sequencing of the PCR product.

Results

Linkage studies

We initially analysed the segregation of four microsatellite markers tightly flanking the *SPG11* gene in 33 kindreds, in which at least two affected patients were sampled. Twelve families were excluded because no common haplotypes segregated with the disease in affected relatives. In 21 families (64%), the reconstruction of the haplotypes was compatible or did not exclude linkage to *SPG11*. In these 21 families, the *SPG11* gene was sequenced.

SPG11 mutation screening

Direct sequencing of the *SPG11* gene was performed in 64 unrelated index patients, including the probands of the 21 putatively linked families mentioned earlier and 43 index patients not analysed by linkage studies. We identified 22 truncating mutations in the index patients of 20 families, 19 were newly identified variants (Table 1). In 14 of these families, the mutations were homozygous. In six kindreds, the patients had two compound heterozygous mutations. The mutations segregated with the disease in the families where this could be tested (Supplementary figure). Unaffected relatives ($n = 47$) never had two mutations in the *SPG11* gene.

Most mutations were nonsense mutations ($n = 4$, three new); small deletions ($n = 13$, 11 new) or insertions (one new). In addition, we identified four new mutations predicted to affect the splicing of the *KIAA1840* mRNA and that were not found on at least 160 and 62 Caucasian and North-African control chromosomes, respectively. In the Israeli-Arab family FSP670, the homozygous c.2833A>G mutation in the last conserved codon of exon 15, leading to the missense variation p.R945G, was also shown to affect the 5′ splice consensus site (score of +2.7 versus +4.9 for the wild-type sequence). This *in silico* prediction was confirmed on mRNA isolated from lymphoblasts of an affected family member (FSP670-5) in which an alternative donor splice site is generated downstream in intron 15 leading to a 65 bp insertion and a premature stop codon (Fig. 1; r.2834 + 1_2834 + 65ins, p.R945GfsX5). The c.2833A>G mutation was also absent from 103 healthy unrelated Palestinians. In families FSP847 and FSP892, homozygous G>A transitions at positions c.869 + 1 and c.2316 + 1 in intron 4 and intron 12 were predicted to strongly alter the consensus sequence score from +9.8 to −0.9 and from +6.2 to −4.5, respectively. The c.869 + 1G>A mutation, found in family FSP847, was also absent from 48 healthy unrelated Argentineans. The single patient from family FSP830, who carried a heterozygous nonsense mutation in exon 6 (c.1282A>T, p.K428X), also carried an A>G transition at position c.6477 + 4 in intron 34 for which the splice score (http://rulai.cshl.edu/new_alt_exon_db2/HTML/score.html) was reduced from +9.6 to +6.6. Living cells were not available, however, to confirm the *in silico* predictions of missplicing in families FSP847, FSP892 and FSP830.

The 22 identified mutations were located in—or close to—15 different exons throughout the gene, from exon 1 to exon 37. However, two of these mutations were found in more than one family. Mutation c.6100C>T/p.R2034X was found in four different kindreds from Algeria, Morocco and Tunisia and was previously reported in three North African families (Stevanin *et al.*, 2007). Portions of the haplotypes reconstructed with four closely flanking markers were similar in the four new kindreds and in families previously reported, indicating a common ancestral mutational event (Table 2). The new mutation c.6737_6740delTTGA/p.I2246_E2247>S2246fsX was found in two families from

Table 1 *SPG11* mutations

Family	Inheritance	Consanguinity	Origin	Exon/intron	Mutation (s)
Homozygous non-sense mutations					
FSP831	AR	yes	Portugal	Exon3	c.529_533delATATT, p.I177SfsX178
SPDI99	AR	yes	Turkey	Exon4	**c.704_705delAT, p.H235RfsX246**
FSP870	AR	yes	Tunisia	Exon4	c.733_734delAT, p.M245VfsX246
FSP393	AR	yes	Portugal	Exon6	**c.1235C>G, p.S412X**
FSP838	Isolated	yes	Saudi Arabia	Exon30	**c.5769delT, p.SI923RfsX1950**
FSP400	AR	yes	Algeria	Exon32	c.6100C>T, p.R2034X
FSP792	AR	yes	Morocco	Exon32	c.6100C>T, p.R2034X
FSP845	Isolated	yes	Morocco	Exon32	c.6100C>T, p.R2034X
FSP881	AR	yes	Tunisia	Exon32	c.6100C>T, p.R2034X
FSP920	AR	yes	Japan	Exon36	**c.6737_6740delTTGA, p.I2246SfsX2260**
FSP75	AR	no	Portugal	Exon37	**c.6832_6833delAG, p.S2278LfsX2338**
Homozygous splice site mutations					
FSP847	AR	yes	Argentina	Intron4	**c.869+1G>A, r.?**
FSP892	Isolated	no	Norway	Intron12	**c.2316+1G>A, r.?**
FSP670	AR	yes	Isarelian-Arab	Exon15	**c.2833A>G, p.R945GfsX950, r.2834_2835ins2834+1_2834+65**
Compound heterozygous mutations					
FSP830	Isolated	no	Portugal	Exon6	**c.1282A>T, p.K428X**
				Intron34	**c.6477+4A>G, r.? (splicing)**
FSP343	AR	no	Algeria	Exon7	**c.1549_1550delCT, p.L517LfsX556**
				Exon36	c.6737_6740delTTGA, p.I2246SfsX2260
FSP522	Isolated	no	France	Exon7	**c.1471_1472delCT, p.L491DfsX556**
				Exon30	**c.5532_5533delCA, p.SI844SfsX1857**
SAL646	Isolated	no	France	Exon8	**c.1668delT, p.F556LfsX577**
				Exon36	**c.6739_6742delGAGT, p.E2247LfsX2260**
FSP683	Isolated	no	Romania	Exon10	**c.1951C>T, p.R651X**
				Exon31	**c.5989_5992delCTGT, p.LI997MfsX2056**
FSP398	AR	no	Poland-Israel	Exon25	**c.4307_4308delAA, p.QI436RfsX1442**
				Exon31	**c.5986_5987insT, p.CI996LfsX1999**

New mutations are indicated in bold.

Japan (homozygous) and from Algeria (heterozygous) associated with different haplotypes as expected. In addition, the c.529_533delATATT/p.I177_I178del>S177fsX mutation (Stevanin *et al.*, 2007), previously found in two Portuguese families, was found in another kindred from the same country (FSP831), associated with the same haplotype (Table 2). In contrast, the c.733_734delAT/p.M245VfsX mutation, previously found on two different ancestral chromosomes in Italian and French families (Del Bo *et al.*, 2007), was homozygous in patients from a Tunisian kindred associated with different haplotypes, suggesting independent mutational events or a very ancient mutation.

Four exonic nucleotide variants present in patients but also in >2% of control chromosomes from France and North Africa are likely to be polymorphisms: c.808G>A/p.V270I (1.5 versus 2.3% in controls), c.1388T>C/p.F463S (47 versus 51%), c.3420G>A/p.L1140L (2.3 versus 3.3%) and c.7023C>T/p.Y2341Y (1.5 versus 7.1%). The p.F463S and p.L1140L variants have already been described in the NCBI (http://www.ncbi.nlm.nih.gov) and Ensembl (http://www.ensembl.org) human genome databases, and the silent changes at residues 1140 and 2341 occurred in the presence of homozygous truncating mutations in the *SPG11* gene. None of them were shown to modify splice sites. Three additional intronic polymorphisms were detected at positions –139A>G and –141A>C upstream exon 8, and +62C>T downstream exon 37 but were not predicted to cause missplicing of the *SPG11* gene.

Clinical characteristics of the 20 new SPG11 families (38 patients)

Six families were North African (two Algerian, two Tunisian and two Moroccan), eight European (four from Portugal, two from France, one from Romania and one from Norway), four Middle-Eastern (two Israeli, one of which of Arabic origin, one Turkish and one Saudi-Arabian) and one each from Argentina and Japan.

Most of the families (65%) had a clear autosomal recessive mode of inheritance, whereas seven index patients (35%), including five without consanguinity, had no family history of neurological disorders.

Age at onset in 37 SPG11 patients ranged from 2 to 27 with a mean of 14.0 ± 5.9 years. Onset was, in most cases, characterized by gait disorders (30/38, 79%), or less frequently by mental retardation (6/38, 16%), rarely dysarthria and tremor (one each). After a mean disease duration of 14.9 ± 6.6 years (range: 2–35), all patients had a

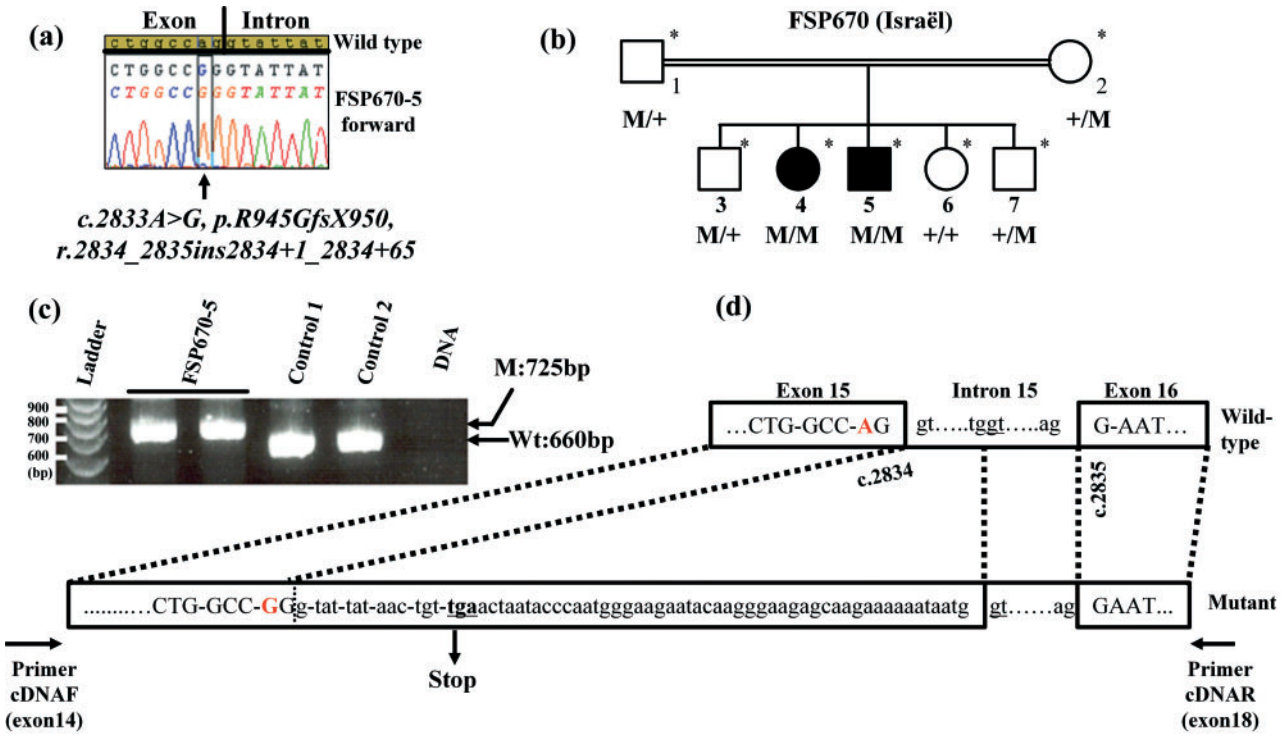

Fig. 1 Mutation c.2833A>G in family FSP670 alters *SPG11* mRNA splicing. (**A**) The electrophoregram shows the c.2833A>G mutation. (**B**) Pedigree and segregation of the mutation in the family. Square symbols represent men, the circles represent women. The filled symbols are affected individuals. The numbers are an internal reference for each sampled individual. Stars indicate sampled subjects. M = mutation; + = wild type. (**C**) Agarose gel separation of the PCR products generated from *SPG11* cDNA from an affected subject and controls showing abnormal processing of the mRNA (**D**) Graphical representation of the effect of the mutation. Exons are boxed. An alternative donor splice site in intron 15 is used in the mutant allele leading to a 65 bp insertion and a premature stop codon.

severe clinical picture that included progressive spastic paraplegia (Table 3): most were at least wheelchair bound (20/38, 53%) or needed assistance for walking (6/38, 16%), but 12 could still walk without help (Fig. 2). While only 12% of the patients were confined to a wheelchair or bedridden after <10 years of disease, 60% were in this condition after 18 years of evolution (Fig. 2). Patients were wheelchair bound after a mean disease duration of 16.5 ± 5.8 years (range 9–35, $n = 20$). Lower limb spasticity was severe in 25/37 (67%), associated with severe weakness in 19/37 (51%). Distal or generalized wasting was also noted in 20/38 (53%). Dysarthria was frequently observed ($n = 16/38$, 42%). Mental retardation, illustrated by learning difficulties in childhood, was present in 12 patients and confirmed in eight who had a mean IQ of 58 ± 9 (range: 45–69). In addition, in 80% (24/30) of the patients, cognitive decline was evident on examination and worsened with time. MMSE scores were low in 4/5 patients tested (<23/30). Only one patient, who had the shortest disease duration (FSP683-3, 2 years), had no mental retardation and cognitive decline. Two patients underwent detailed neuropsychological evaluation (FSP522-1 and FSP75-21). The non-verbal evaluation of global cognitive efficiency in patient FSP522-1 was normal (PM38 = 46/60), but she had a severe memory impairment (Wechsler Memory Quotient = 72/140) associated with reduced verbal fluency and an attention deficit indicative of executive dysfunction. A second evaluation, 5 years later, showed deterioration of her cognitive status. Patient FSP75-21, who had mental retardation (IQ = 56), showed a MMSE score of 21/30 at 35 years with psychiatric and cognitive difficulties that included auditory hallucinations and executive dysfunctions.

Cerebellar ocular signs such as abnormal saccadic pursuit and nystagmus were noted in seven patients, most of whom had disease durations >15 years (5/21 versus 2/17). There was *pes cavus* in eight patients, scoliosis in five and other signs were occasionally observed: parkinsonism, orthostatic hypotension, macular excavation or degeneration, strabismus. Four patients, all with disease durations of >18 years, had swallowing difficulties.

Interestingly, ENMG detected lower motor neuron involvement in 13/16 (81%) after a mean disease duration of 14.4 ± 4.9 years (Table 4). In two patients, there was clear anterior horn involvement, while in the others there was axonal neuropathy. Brain MRI showed a TCC (20/21, 95%), with cortical atrophy (17/21, 81%) and associated with diffuse white matter hyperintensities on T2 images (13/19, 69%). The atrophy of the *corpus callosum* was found in all but one patient (FSP400-5, 7-year disease duration), but with variable intensity (Fig. 3). Leucoencephalopathy was periventricular and confluent, and its severity increased

Table 2 Haplotypes of four close flanking markers segregating with the recurrent mutations in the *SPG11* gene in this study and in previous reports (Stevanin *et al.*, 2007; Del Bo *et al.*, 2007)

	Stevanin *et al.*, 2007									
Family	FSP400	FSP446	FSP88I	FSP792	FSP845	FSP22I	FSP732	FSP920	FSP343
Origin	Algeria	Morocco	Tunisia	Morocco	Morocco	Algeria	Algeria	Japan	Algeria
D15S78I	I85	I85	I85	I85	I85	I85	I85	I83	I85/I87
D15S537	I80	I80	I80	I76	I76	I76	I76	I80	I84
SPG11	*c.6100C>T*	*c.6100C>T*	*c.6100C>T*	*c.6100C>T*	*c.6100C>T*	*c.6100C>T*	*c.6100C>T*	*c.6737.6740delTTGA*	*c.6737.6740delTTGA*
D15S516	I91	I91	I91	I91	I91	I91	I91	I95	I95
D15S659	I95	I79	I79	I79	I79	I79	I75	I75	I87

	Stevanin *et al.*, 2007				DelBo *et al.*, 2007			
Family	FSP83I	FSP754	FSP386	FSP386	FSP870	FSPII7	DelBo	
Origin	Portugal	Portugal	Portugal	Portugal	Tunisia	France	Italy	
D15S78I	I85	I85	I85	I85	I87	I85	ND	
D15S537	I72	I72	I72	I72	I80	I72	I89	
SPG11	*c.529.533delATATT*	*c.529.533delATATT*	*c.529.533delATATT*	*c.529.533delATATT*	*c.733.734delAT*	*c.733.734delAT*	*c.733.734delAT*	
D15S516	I95	I95	I95	I93	I95	I95	ND	
D15S659	203	203	ND	ND	I95	I79	ND	

ND = not done. Conserved regions are highlighted in grey. Genotypes are indicated in base pairs.

with disease duration. In mild cases, only frontal and occipital periventricular damage was seen (Fig. 3). Finally, visual evoked potentials were abnormal in three out of five patients, indicating an even more diffuse distribution of the lesions.

Discussion

The identification of 22 different truncating mutations (19 new) distributed throughout the *SPG11* gene (Fig. 4) emphasizes the need to analyse the whole gene in clinical practice. Only two of these mutations were found in more than two families in this study and previous studies, suggesting regional founders in these populations (Stevanin *et al.*, 2007): the recurrent mutation c.6100C>T/p.R2034X in families from North Africa where it accounted for 70% of the reported cases (7/10 mutated families); the c.529_533delATATT/p.I177_F178>S177fsX mutation in Portuguese families (3/6 mutated families). Conserved haplotypes for flanking microsatellite markers were associated with these mutations.

Most of the 20 new SPG11 families originated from the Mediterranean basin, but mutations were also found in families from Scandinavia, Japan and South America, indicating a worldwide distribution of this clinico-genetic entity, as previously suggested (Shibasaki *et al.*, 2000; Casali *et al.*, 2004; Winner *et al.*, 2006; Stevanin *et al.*, 2006; Olmez *et al.*, 2006).

When the eleven previously reported cases (Stevanin *et al.*, 2007) from our series are taken into account, *SPG11* mutations are found in ~26% (9/35) of apparently sporadic HSP with TCC patients and ~40% (22/53) of subjects with complex AR-HSP. Interestingly, the frequency varies widely according to the phenotype (Table 5). *SPG11* mutations were found in 59% of patients with TCC and mental impairment collected by our network, a frequency very close to the 41–77% of families from Italy, Japan and Mediterranean countries found in previous linkage analyses (Shibasaki *et al.*, 2000; Casali *et al.*, 2004; Stevanin *et al.*, 2006). Mutations in *SPG11* accounted for only a single family (1/22, 4.5%) of the subgroup of patients with HSP and cognitive impairment without TCC, but patients from this kindred had mild white matter changes and cortical atrophy after a short disease duration of 7 years. SPG11 is therefore the major identified cause of HSP-TCC and, when taking into account the proportion of 1/3 of HSP-TCC among ARHSP (Franca *et al.*, 2007), SPG11 is responsible for ~21% of families with ARHSP, making it the most frequent cause of this disease.

The clinical features of the SPG11 patients studied here were similar to previous reports (Shibasaki *et al.*, 2000; Casali *et al.*, 2004; Winner *et al.*, 2006; Stevanin *et al.*, 2006; Lossos *et al.*, 2006), with a broader range of ages at onset (2–27 years). SPG11 is severe since patients were wheelchair bound after a mean disease duration of 16.5 ± 5.8 years (range 9–35, $n = 20$) compared to 26.6 ± 15 years (range

Table 3 Clinical features of 38 patients with mutations in the *SPG11* gene

Patient (Sex)	Age at onset (years)	Symptoms at onset	Age at exam (years)	Disease duration (years)	Severity/leg spasticity	Weakness/wasting	Pyramidal syndrome [UL/knee/plantar reflexes]	Mental impairment	Cognitive decline	Other signs or symptoms
FSP831-5 (M)	6	Learning difficulties followed by spastic gait at age 15	31	25	Bedridden/ severe	Severe/none	++ ++ ↑↑	Yes	Yes	Pes cavus, swallowing difficulties
SPDI99-1 (F)	12	Tremor at rest and action	28	16	Wheelchair at age 22/severe	Severe/moderate	++ + ↑↑	Yes mild	ND	Parkinsonism with severe akinesia, rigidity and tremor
SPDI99-15 (M)	Childhood	Stiff legs	21	NA	Walking aid at age 20/severe	Moderate/none	ND ++ (-at ankles) ↑↑	Yes (MMSE 21/30)	Yes	Parkinsonism with rest tremor, strabism
FSP870-17 (M)	15	Stiff legs	25	10	Gait possible without help/severe	Severe/yes	N ++ ↑↑	Yes (MMSE<15/30)	Yes	Pes cavus, facial dystonia,renal lithiasis
FSP870-20 (F)	17	Weakness legs	28	11	Wheelchair at age 28/severe	Severe/none	+ ++ ↑↑	Yes	No	Dystonia of face and tongue
FSP870-27 (F)	14	Stiff legs	29	15	Wheelchair at age 27/severe	Severe/none	+ ++ ↑↑	Yes	No	None
FSP870-28 (F)	20	Weakness legs	42	22	Wheelchair at age 38/severe	Moderate/none	+ + ↑↑	Yes	No	None
FSP393-11 (F)	7	Learning difficulties	25	18	Gait possible without help/ moderate	Mild/none	++ ++ ↑↑	Yes	Yes	Spastic dysarthria
FSP393-12 (M)	7	Learning difficulties	24	17	Gait possible without help/ moderate	Mild/none	++ ++ ↑↑	Yes	Yes	Spastic dysarthria, decreased vibration sense
FSP838-1 (F)	13	Stiff legs	22	9	Walking aid/mild	Moderate/none	N ++ ↑↑	Learning difficulties at age 15	ND	None
FSP400-5 (F)	5	Leg weakness	12	7	Gait possible without help/ moderate	Moderate/ generalized	++ ++ ↑↑	No	Yes	Spastic dysarthria
FSP400-10 (M)	2	Delayed walking acquisition, stiff legs	13	11	Gait possible without help/ moderate	Moderate/none	++ ++ ↑→	Yes (learning difficulties)	Yes	Spastic dysarthria, scoliosis
FSP792-4 (M)	19	Stiff legs	32	13	Gait possible without help/ severe	Severe/moderate legs mild arms	N ++ ↑↑	Yes (IQ = 45, MMSE = 23/30)	Yes	None
FSP792-5 (F)	17	Stiff legs	37	20	Walking aid/ severe	Severe/mild distal	N ++ ↑↑	Yes (IQ = 47)	Yes	None

FSP845-7 (M)	16	Stiff legs	29	13	Wheelchair/ severe	Severe/mild	N ++ ↑↑	Yes (MMSE = 15/30)	Yes	None
FSP881-143 (M)	16	Weakness legs	26	10	Wheelchair/ severe	Severe/mild	N ++ ↑↑	No	ND	None
FSP881-144 (M)	14	Weakness legs	30	16	Wheelchair/ severe	Severe/severe	N ++ ↑↑	Yes mild	ND	Pes cavus, scoliosis
FSP881-145 (F)	16	Weakness legs	26	10	Walking aid/ severe	Severe/none	++ ++ ↑↑	No	ND	None
FSP920-1401 (M)	15	Stiff legs	26	11	Wheelchair/ severe	Moderate/ generalized mild	+ + ↑↑	Yes (IQ = 63)	Yes	Slow speech, pes cavus, obesity
FSP920-1402 (M)	9	Stiff legs	18	9	Wheelchair at age 25/na	ND/none	+ + ↑↑	Yes (IQ = 63)	Yes	Pes cavus
FSP75-21 (F)	2	Tip toe walking	24	22	Gait possible without help/ severe	Moderate/severe	++ ++ ↑↑	Yes (IQ = 52)	Yes hallucinations at age 25	Nystagmus, hypertrichosis, dysarthia, orthostatic hypotension
FSP75-43 (M)	7	Learning difficulties	33	26	Wheelchair/ severe	Severe/generalized	++ ++ (- at ankles) ↑↑	Yes (IQ=64)	Yes	Spastic dysarthria
FSP847-22 (M)	15	Unsteadiness, stiff legs	30	15	Wheelchair/ severe	Severe/generalized	++ ++ ↑↑	Yes	ND	Dysarthria, saccadic pursuit, vertical and horizontal gaze limitations, scoliosis
FSP847-23 (M)	16	Unsteadiness, stiff legs	29	13	Wheelchair/ severe	Severe/generalized	++ ++ ↑↑	Yes	ND	Dysarthria, saccadic pursuit, vertical and horizontal gaze limitations, scoliosis
FSP847-25 (F)	15	Unsteadiness, stiff legs	22	7	Gait possible without help/ moderate	Moderate/mild distal LL	++ ++ ↑↑	No	ND	Dysarthria, saccadic pursuit
FSP892-3 (M)	22	Dysarthria	30	8	Gait possible without help/mild	Moderate/none	N ++ ↑↑	Yes	Yes	Spastic dysarthria
FSP670-4 (F)	12	Cognitive difficulties	31	19	Wheelchair/severe	Severe/none	+ ++ ↑↑	Yes (IQ = 61)	Yes	High arched palate, hyperpigmented skin
FSP670-5 (F)	12	Cognitive difficulties	30	18	Wheelchair/ Severe	Severe/none	+ ++ ↑↑	Yes (IQ = 69)	Yes	

(continued)

Table 3 Continued

Patient (Sex)	Age at onset (years)	Symptoms at onset	Age at exam (years)	Disease duration (years)	Severity/leg spasticity	Weakness/wasting	Pyramidal syndrome [UL/knee/plantar reflexes]	Mental impairment	Cognitive decline	Other signs or symptoms
FSP830-5 (F)	27	Unsteadiness	43	16	Wheelchair at age 40/severe	Severe/Mild and distal	++ ↑↑	No	Yes	Macular degeneration
FSP343-1085 (M)	16	Stiff legs	33	17	Walking aid/severe	Moderate/mild UL	+ ++ ↑↑	Yes (learning difficulties)	Yes	Dysarthria, pes cavus, macular excavation
FSP343-1081 (F)	5	Leg weakness	40	35	Wheelchair/ moderate	Severe/none	N ++ ↑↑	No	No	Meningoencephalitis after measles and sequella (left hemiparesis and epilepsy)
FSP343-1084 (M)	22	Weakness legs	37	15	Walking aid/ moderate	Moderate/none	+ ++ ↑↑	No	No	Pes cavus, dysarthria, nystagmus, macular excavation
FSP522-1 (F)	19	Stiff legs	25	6	Gait possible without help/ moderate	Moderate/none	+ ++ ↑↑	No (MMSE = 26/30)	Yes (memory and executive functions)	Abnormal fat distribution, orthostatic hypotension
SAL646-6 (F)	15	Stiff legs	23	8	Gait possible without help/ moderate	Mild/none	+ ++ ↑↑	Yes	Yes	Pes cavus, Spastic dysarthria, Impaired pin-prick sense, deceased at age 36
FSP683-3 (M)	18	Stiff legs	20	2	Gait possible without help/ moderate	Moderate mild UL/mild LL	+ + ↑↑	No	No	Scoliosis
FSP398-15 (F)	23	Gait difficulties	42	19	Wheelchair/ severe	Moderate/severe	+ ++ (- at ankles) NA	No	Yes	Spastic dysarthria, saccadic pursuit, swallowing difficulties
FSP398-17 (F)	17	Stiff legs	38	21	Wheelchair at age 26/severe	Mild/severe	++ ++ NA	No	Yes	Dysarthria, urinary incontinence, swallowing difficulties
FSP398-19 (F)	15	Gait difficulties	35	20	Bedridden/ severe	Severe/severe	++ ++ (- at ankles) NA	No	Yes	Strabism, spastic dysarthria, swallowing difficulties, saccadic pursuit

M = male; F = female; ND = not done; NA = not assessed; N = normal; UL = upper limbs; LL = lower limbs; IQ = intellectual quotient; MMSE = Mini Mental State Evaluation; + = enhanced; ++ = increased. Left and right plantar reflexes are indicated as: '↑' = extensor, '→' = indifferent.

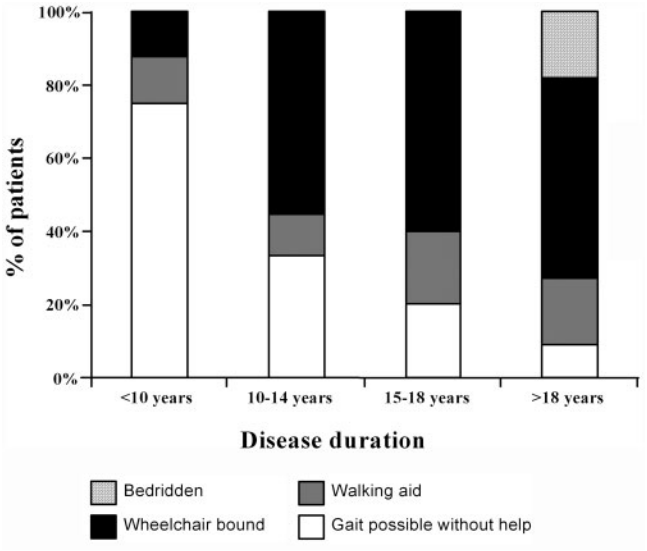

Fig. 2 Severity according to disease duration in SPG11 patients.

5–49, $n = 5$) in SPG4 patients (Depienne *et al.*, 2006, 2007). Mental retardation or cognitive impairment and atrophy of the *corpus callosum* are the hallmarks of this disorder, but they may be lacking in patients with short disease durations (<10 years). Another frequent sign is axonal neuropathy, sometimes associated with anterior horn signs, observed in 81% of affected subjects. This is indicative of lower motor neuron degeneration and may clinically mimic amyotrophic lateral sclerosis when wasting is marked. White matter abnormalities are also frequently observed on MRI (69%). They start in the periventricular regions close to the frontal and occipital horns and increase in frequency and severity with disease duration, which may lead to a misdiagnosis of leucodystrophy. Finally, cerebellar ocular signs may also occur as the disease progresses.

The phenotype of 21 patients from 15 kindreds with TCC and mental impairment but no mutations in *SPG11* did not differ from SPG11 patients except for an earlier mean age at onset of 9.6 ± 13.0 (range: 6 months to 50 years). Gait instability was the sign at onset in all patients

Table 4 Paraclinical investigations in 27 SPG11 patients

Individual	Disease duration (years)	Cerebral MRI			ENMG	Evoked potential
		Cortical atrophy	TCC	WMA	(N neuropathy)	(V visual, A auditory, S somatosensory)
FSP522-1	6	–	+	–	Axonal sensory-motor N	A,V Normal
FSP400-5	7	+	–	+ (mild)	Normal	S abnormal, V normal
FSP847-25	7	+	+	NA	ND	ND
SAL646-1	8	ND	ND	ND	Axonal sensory-motor, neurogenic pattern	V abnormal, A, S normal
FSP892-3	8	–	+	–	Axonal motor N	ND
FSP670-5	8	+ (mild frontal)	+	+	ND	ND
FSP838-1	9	+	+	+ (mild)	Normal	ND
FSP920-1402	9	–	+	–	ND	ND
FSP670-4	9	ND	ND	ND	Axonal sensory-motor N	V abnormal
FSP920-1401	11	–	+	–	ND	ND
FSP870-20	11	ND	ND	ND	Axonal Motor N	ND
FSP792-4	13	+	+	+	Axonal motor N	ND
FSP845-7	13	+	+	+	ND	ND
FSP847-23	13	+	+	NA	ND	ND
SPDI99-15	15	+	+	+	Axonal sensory-motor N (biopsy: neurogenic atrophy)	ND
FSP683-3	15	–	+	+ (posterior)	ND	ND
SPDI99-1	16	+	+	+	Axonal sensory-motor N	ND
FSP830-5	16	+	+	+	Axonal motor N	V abnormal
FSP393-12	17	ND	ND	ND	Anterior horn	ND
FSP343-1085	17	+ (mild)	+	–	Axonal sensory-motor N	ND
FSP881-144	19	ND	ND	ND	Axonal sensory-motor N	S normal
FSP792-5	20	+	+	+	ND	ND
FSP75-21	20	+ (mild, megaciterne posterior)	+	-	ND	ND
FSP398-17	21	+	+	+	ND	ND
FSP831-5	15	+	+	+	Normal	V,A,S normal
FSP75-43	26	+	+	+ (bifrontal)	Anterior horn involvement	ND
FSP343-1081	35	+ (sequellae fronto-parietal lesion)	NA	NA	ND	ND

+ = Present; – = absent; ENMG = electroneuromyography; NA = not assessed; ND = not done; WMA = white matter abnormalities; TCC = thin *corpus callosum*.

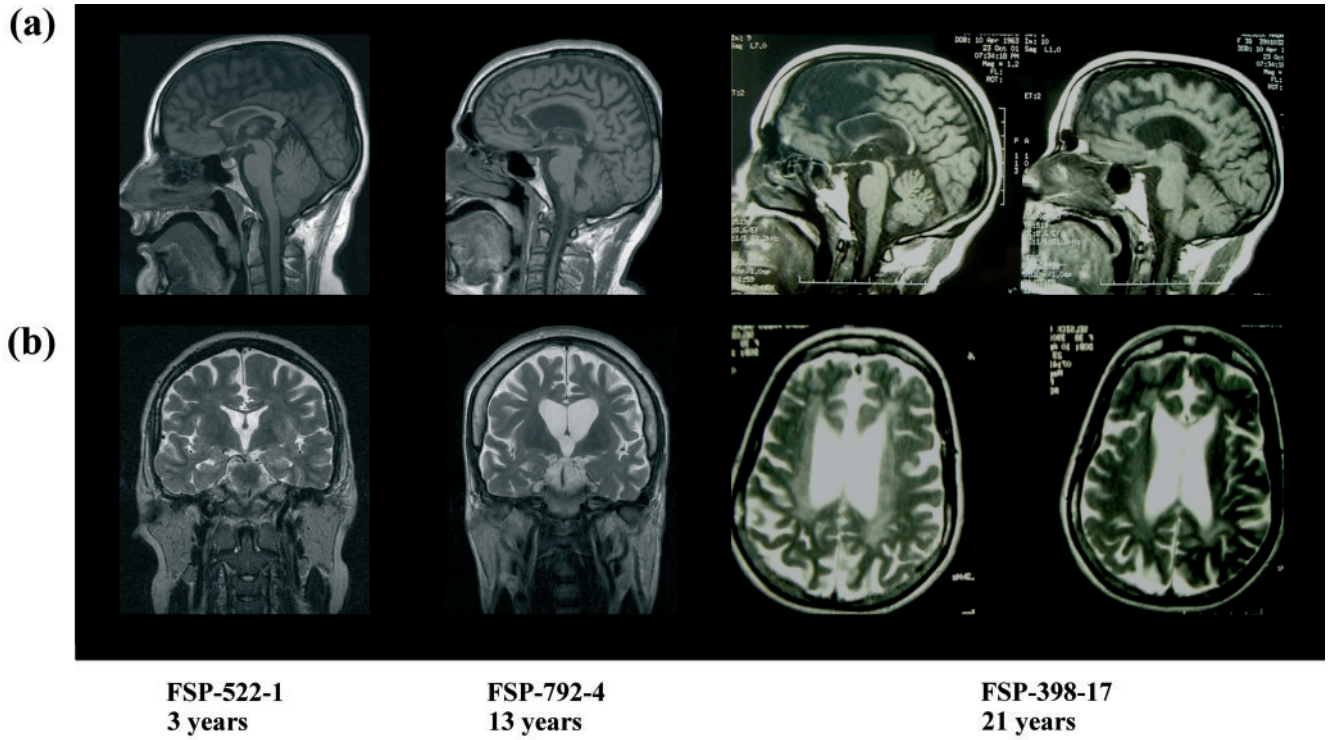

Fig. 3 Brain MRI images of three patients with different disease durations. (**A**) T1-weighted sagittal image showing thin *corpus callosum* and global cortical atrophy, (**B**) T2–Fast Spin Echo weighted axial and coronal images showing periventricular hyperintensities of variable severity according to disease duration.

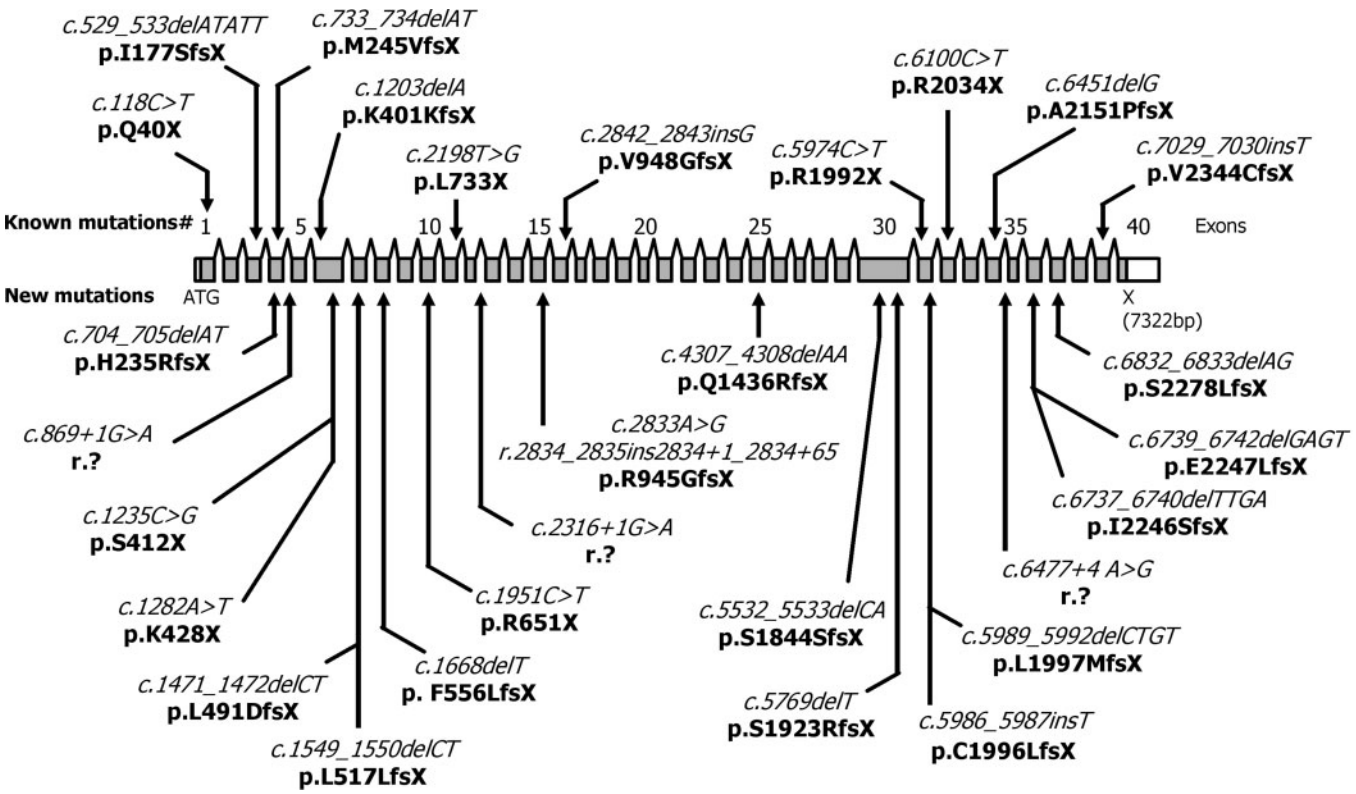

Fig. 4 Schematic representation of the SPG11 gene showing the location of the known (up) and new (down) mutations. # reported by Stevanin *et al*., 2007 and DelBo *et al*., 2007.

Table 5 Frequency of *SPG11* mutations according to the phenotype

	Phenotypes	HSP associated with				Sum
		TCC and cognitive impairment	TCC without cognitive impairment	cognitive impairment (MRI not done)	cognitive impairment without TCC	
This study	Number of index cases	26	11	17	22	76
	Excluded by linkage analysis/Nb families analyzed	5/14	0/3	1/6	6/10	12/33
	Mutated index cases/Nb sequenced cases	11/21	4/11	4/16	1/16	20/64
	SPG11 frequency	11/26 (42%)	4/11 (36%)	4/17 (23%)	1/22 (4.5%)	20/76 (20%)
This study and Stevanin *et al*. 2007		*22/37 (59%)*	*4/12 (33%)*	*4/17 (23%)*	*1/22 (4.5%)*	*31/88 (35%)*

HSP = hereditary spastic paraplegia; TCC = thin *corpus callosum*

and cerebellar signs were present in 5. Eight of these 15 individuals were sporadic.

In summary, the presence of HSP-TCC is the best single indicator that *SPG11* should be tested in patients with onset in the first to third decade, but the presence of one or more other signs, such as mental retardation and later cognitive deterioration, lower motor neuron involvement and white matter lesions, increases the chance of identifying *SPG11* mutations. Additionally, evidence of white matter abnormalities in the periventricular regions increases even further the probability that *SPG11* is the cause of the disease, rather than other causes of leucodystrophy. HSP mainly affects the corticospinal axons by a dying back mechanism but lesions in SPG11 are wider, as suggested by the identification of TCC and other white matter abnormalities, signs of lower motor neuron degeneration, cerebellar ataxia and abnormal visual evoked potentials. Further studies are now required to understand the effects of these mutations, all truncating, causing the loss of spatacsin function in upper and lower motor neurons as well as in other regions of the nervous system.

Supplementary materials

Supplementary materials are available at *Brain* online.

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Appendix

Members of the Spastic Paraplegia and ATAXia network (SPATAX): Dr A. Durr (Hôpital Pitié-Salpêtrière, Paris, France), Pr B. Fontaine (Hôpital Pitié-Salpêtrière, Paris, France), Pr J.P. Azulay (Hôpital de la Timone, Marseille, France), Pr A. Benomar (CHU, Rabat, Morocco), Pr E. Bertini (Osp. Bambino Gesù, Roma, Italy), Dr O. Boespflug-Tanguy (Faculté de Médecine, Clermont-Ferrand, France), Pr P. Coutinho (Hospital San Sebastião, Santa Maria da Feira, Portugal), Pr A. Filla (Università Degli Studi Di Napoli Federico II, Napoli, Italy), Pr D. Hannequin (Hôpital Charles Nicolle, Rouen, France), Dr A. Hamri (Hôpital Benbadis, Constantine, Algeria), Pr Michel Koenig (IGBMC, Illkirch, France), Pr P. Labauge (Hôpital Caremeau, Nimes, France), Pr A. Lossos (Hadassah Hebrew University Hospital, Jerusalem, Israel), Pr A. Megarbane (Université Saint-Joseph, Beirut, Lebanon), Pr J.E. Nielsen (The Panum Institute, Copenhagen, Denmark), Pr A.M. Ouvrard Hernandez (CHU, Grenoble, France), Dr E. Reid (Addenbrooke's Hospital, Cambridge, UK), Dr D. Rodriguez (Hôpital St Vincent De Paul, Paris, France) Pr S. Roumani (Dpt of Neurology, Damascus, Syria), Pr M. Salih (University Hospital, Ryadh, Saudi Arabia), Pr J. Sequeiros (University of Porto, Porto, Portugal), Dr C. Tallaksen (Ullevål University Hospital, Oslo, Norway), Pr M. Tazir (CHU Mustapha, Algiers, Algeria), Pr F. Tison (Groupe Hospitalier Sud, Pessac, France), Dr C. Goizet (Hôpital Pellegrin, Bordeaux, France), Dr E.M. Valente (Istituto Di Genetica Medica, Roma, Italy), Pr N. Wood (The National Hospital, London, UK), Dr C. Verny (CHU, Angers, France) and Pr T. Warner (Royal Free and University College Medical School, London, UK).