Complicated spastic paraplegia in patients with AP5Z1 mutations (SPG48)

**ABSTRACT**

**Objective:** Biallelic mutations in the AP5Z1 gene encoding the AP-5 ζ subunit have been described in a small number of patients with hereditary spastic paraplegia (HSP) (SPG48); we sought to define genotype-phenotype correlations in patients with homozygous or compound heterozygous sequence variants predicted to be deleterious.

**Methods:** We performed clinical, radiologic, and pathologic studies in 6 patients with biallelic mutations in AP5Z1.

**Results:** In 4 of the 6 patients, there was complete loss of AP-5 ζ protein. Clinical features encompassed not only prominent spastic paraparesis but also sensory and motor neuropathy, ataxia, dystonia, myoclonus, and parkinsonism. Skin fibroblasts from affected patients tested positive for periodic acid Schif and autofluorescent storage material, while electron microscopic analysis demonstrated lamellar storage material consistent with abnormal storage of lysosomal material.

**Conclusions:** Our findings expand the spectrum of AP5Z1-associated neurodegenerative disorders and point to clinical and pathophysiologic overlap between autosomal recessive forms of HSP and lysosomal storage disorders. *Neurol Genet* 2016;2:e98; doi: 10.1212/NXG.0000000000000098

**GLOSSARY**

HSP = hereditary spastic paraplegia; NCS = nerve conduction study; PAS = periodic acid-Schiff; PSP = progressive supranuclear palsy; SCA = spinocerebellar ataxia.

AP-5 is an adaptor protein that facilitates vesicular-mediated intracellular sorting and trafficking of transmembrane cargo proteins. AP-1 and AP-2 are the cardinal members of this protein family and assist in clathrin-based receptor-mediated endocytosis and intracellular trafficking, respectively. AP-5 acts independently of clathrin in the endolysosomal system and is comprised of β5, ζ5, μ5, and σ5 subunits. Although the identity of AP-5 cargo(es) remains unknown, this adaptor protein clearly has an important role in normal physiology, evidenced by the recent identification of biallelic mutations in the ζ subunit (AP5Z1) in some patients with hereditary spastic paraplegia (SPG48).1–3 Recent findings indicate that 2 hereditary spastic paraplegia (HSP)-associated proteins, SPG11/spatacsin and SPG15/spastizin, interact with AP-5,4 suggesting that common molecular mechanisms may be at work. Patients with autosomal recessive loss-of-function SPG11 or SPG15...
mutations exhibit closely overlapping clinical features, which include thin corpus callosum, retinal abnormalities, sensory and motor neuropathy, mild ataxia, cognitive impairment, and parkinsonism. The parkinsonism in SPG11 and SPG15 patients can be particularly prominent, with some patients presenting with juvenile parkinsonism responsive to dopaminergic therapy.\textsuperscript{5}

We present a series of patients with homozygous or compound heterozygous mutations in \textit{AP5Z1}. Most patients presented with spastic paraparesis. Additional features included ataxia, dystonia, intellectual impairment, myoclonus, and parkinsonism. One patient presented with pure sensory and motor neuropathy. Patient-derived fibroblasts demonstrated an accumulation of autofluorescent and multilamellar storage material. These findings expand the spectrum of \textit{AP5Z1}-associated complicated hereditary spastic paraplegia.

\textbf{METHODS} Skin biopsy was performed, and fibroblast cell lines were established using standard methods. Genomic DNA was extracted from whole blood.

Exome sequencing was performed after target capture using an Agilent SureSelect or Illumina TruSeq kit and run on an Illumina HiSeq2000 or HiSeq2500 as per the manufacturer’s instructions, employing 101-bp paired-end read sequencing. Reads were mapped to the reference genome using the Burrows-Wheeler Aligner and processed using the Genome Analysis Toolkit. Data for patient 1 were analyzed using bam2mpq (e-Methods at Neurology.org/ng). Missense variants were sought in public databases to determine minor allele frequencies (ExAc, EVS) and interrogated in silico to predict the damaging effects (SIFT, PolyPhen-2, Mutation Taster, and CDPred). Sanger sequencing was performed for the confirmation of mutations.

Patient-derived fibroblasts and HeLa M cells were grown in Dulbecco modified Eagle medium, supplemented with 10% (v/v) fetal calf serum (Sigma-Aldrich, St. Louis, MO), 2 mM l-glutamine, 50 U/mL penicillin, and 50 μg/mL streptomycin (Sigma-Aldrich). To analyze proteins levels, fibroblasts were lysed in phosphate-buffered saline containing 0.1% Triton X-100 with (Sigma-Aldrich). To analyze proteins levels, fibroblasts were lysed in

For electron microscopy, cells were grown on plastic dishes and fixed with 1% osmium tetroxide, and 5% glutaraldehyde, and 0.1 M cacodylate buffer pH 7.2) added and fixed using a double-strength fixative (4% paraformaldehyde, ethanol before being embedded in EPON in beam capsules and cured overnight at 65°C. Ultrathin (50–70 nm) conventional sections were cut using a diamond knife mounted to a Reichart Ultracut S ultramicrotome. Sections were collected onto copper grids and stained using lead citrate. They were viewed using an FEI Tecnai transmission electron microscope (Eindhoven, the Netherlands) at 80 kV.

\textbf{Standard protocol approvals, registrations, and patient consents.} Patients were recruited into a local institutional review board and/or ethics committee–approved research protocols, and written informed consent for participation was obtained.

\textbf{Nonsense mutations. Patient 1.} This patient, in his 70s at the time of examination, was born to first-generation immigrant parents who hailed from the same city in Germany, but without known consanguinity. Medical history revealed macrocular degeneration, hypertension, and mild hearing loss that began in his late 50s. The patient presented for evaluation after he developed a stiff, shuffling gait at age 60, leading to frequent tripping and occasional falls. This gradually progressed to the point where he needed a walker to ambulate. He also experienced frequent cramping of the lower limbs. As his gait problems progressed, his family noted facial hypomimia and bradykinesia. He developed a spastic bladder and pain and numbness in both feet.

On examination, the patient exhibited prominent lower extremity spasticity with mild distal muscle weakness and mild weakness of the hip flexors. Cognition was intact. Cogwheel rigidity was evident in the upper limbs, and this increased with reinforcement. He had slow rapid alternating movements, mild dysmetria, and a coarse, low-frequency rest tremor (video 1) in addition to a higher-frequency kinetic tremor. Mild spastic dysthria was evident. Sensory examination revealed loss of vibratory sensation in the great toes. Mild foot dystonia was seen, greater in the left than in the right, with curling of the toes. Gait was both spastic and parkinsonian (video 2).

An EMG/NCS (nerve conduction study) was performed 2 years prior to evaluation and showed slight slowing of Tibial and peroneal motor velocities. Needle EMG showed mild chronic re-innervation in distal leg muscles, sparing the peroneal motor branch of the sciatic nerve. Upper motor neuron involvement was not evident. Together, these findings were consistent with mild, motor greater than sensory polyneuropathy. Ophthalmologic examination showed a best-corrected visual acuity at 20/32 in both eyes and posterior subcapsular cataracts bilaterally. Choroidal depigmentation and pigment clumping around the optic nerves as well as in several areas in the mid-periphery, with thinning of the nerve fiber layers in both eyes was observed when examined with optical coherence tomography. There was also a partial macular hole in the left eye, with thinning of the macular area in both eyes. Brain MRI at age 72 disclosed mild cortical atrophy and periventricular T2 white matter hyperintensities, similar to the “ears of the lynx” sometimes seen in SPG11 and SPG15 (figure 1).

\textbf{Patient 2.} The index patient in a Belgian family with 3 affected siblings (patients 2–4), this gentleman developed spasticity of the lower limbs which began to affect his gait at age 39. His medical history was notable for mild intellectual disability. Over the ensuing decades, he developed urinary incontinence and visual decline and became dependent on a wheelchair to travel long distances.

On examination at age 64, he showed distal muscle wasting more prominently in the lower limbs. Limb ataxia was evident. His deep tendon reflexes were exaggerated, and he had a positive Babinski sign. Vibration sense was impaired. Motor testing revealed distal lower limb weakness. Gait was both spastic and
ataxic. He had cerebellar speech and hypomimia. Ophthalmologic examination showed pigmentary retinopathy (placoid multiform pigment epitheliopathy) (figure 2) and mild cataracts with lens sclerosis bilaterally. Urologic evaluation revealed a spastic bladder. No dementia was evident (Folstein mini-mental status examination score 30).

An EMG/NCS indicated an axonal sensory polyneuropathy. Somatosensory evoked potentials showed an abnormal central

Figure 1 MRI features of AP5Z1-associated complicated spastic paraplegia

(A) Periventricular white matter hyperintensities are common in AP5Z1 patients (blue-white arrows). (B) In some cases, this lends an “ears of the lynx”-like appearance to T2/fluid-attenuated inversion recovery axial images (blue arrows). (C) A “moth-eaten” appearance of the basal ganglia with putaminal rim hyperintensity was noted in several individuals (hatched arrows). (D) Focal atrophy of the body of the corpus callosum led to a distinctive sagittal appearance in several patients (arrowheads), while 2 siblings from the Belgian family exhibited a “hummingbird sign” (focal atrophy of the midbrain; long arrows).
response in the right upper limb. MRI of the brain disclosed white matter lesions affecting the basal ganglia and deep white matter and focal atrophy of the corpus callosum (figure 1), while a full spine MRI was normal. Laboratory testing did not find evidence of abnormalities of lactate, α-fetoprotein, or creatine kinase. Triplet repeat expansion analysis for spinocerebellar ataxia (SCA) 1, 2, 3, 6, and 7 was normal.

**Patient 3.** This 56-year-old sister of patients 2 and 4 began experiencing slowing of movements and gait disturbances at age 50. She had attended a special school because of intellectual disability and worked in an adapted environment. In her mid-50s, she began to exhibit progressive difficulty with both her vision and walking and began to rely on walking aids and eventually a wheelchair for long distances.

Her neurologic examination disclosed visual impairment but otherwise unremarkable cranial nerves. Her speech was remarkable for scanning dysarthria. Her movements were bradykinetic, and she exhibited limb dystonia. Finger-to-nose and heel-to-shin testing disclosed limb dysmetria. The patient’s reflexes were brisk in her lower limbs, and she demonstrated a Babinski sign bilaterally. She showed impaired vibration sense, and her gait was both spastic and ataxic. She was treated with pramipexole and rasagiline with little improvement. She developed urinary incontinence, and urological workup disclosed a spastic bladder. No dementia was evident. Ophthalmologic examination revealed glaucoma and bilateral pigmentary retinopathy (placoid multiform pigment epitheliopathy) with mild cataracts and lens sclerosis in both eyes. The EMG/NCS was consistent with an axonal polyneuropathy, and her Brain MRI showed white matter hyperintensities (figure 1).

**Patient 4.** This brother of patients 2 and 3 sought medical evaluation for progressive visual loss. He had a longstanding history of mild intellectual disability. On examination, his speech was found to be normal but saccades were slowed. His reflexes were accentuated in the lower limbs, and he had a bilateral extensor toe response. Gait was spastic–ataxic, and he had dysdiadochokinesia in both hands. Strength, coordination, and sensation were normal on bedside examination. No dementia was evident (Folstein mini-mental status examination score 30).

Ophthalmologic examination revealed pigmentary retinopathy. His brain MRI showed white matter hyperintensities similar to those of his siblings (figure 1).

**Missense mutations. Patient 5.** This woman in her 50s was evaluated for chronic sensory loss and weakness. The patient was adopted; her biological mother had become pregnant as a result of incest. The patient’s birth was uneventful. She began walking at the age of 14 months. The remainder of her early development was felt to be normal, although she ran slowly and struggled to keep pace with her peers. She suffered from poor balance and fell frequently. Early evaluations disclosed a steppage gait beginning in childhood. She sustained periodic injuries in adolescence and young adulthood. In one instance, she burned her hands badly after holding a hot plate without recognizing the high temperature. If she closed her eyes, she would fall. By the time she finished high school, her ankles had become weak, but she was still able to walk upstairs without using rails.

Her symptoms accelerated in her late 20s. She began to fall more frequently and started to use ankle–foot orthotics. She could no longer run. She could not walk on her heels or toes at that point. At age 45, she started to use a cane. Two to 3 years later, she began to experience difficulties with writing, buttoning, and cutting food, with frequent cramping of the hands.
### Table: Clinical features of AP5Z1 patients

<table>
<thead>
<tr>
<th>Patient</th>
<th>Mutation</th>
<th>Gait impairment</th>
<th>Ataxia</th>
<th>Spastic paraplegia</th>
<th>Other</th>
<th>Eye findings</th>
<th>MRI</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(p.Q578*) homozygous</td>
<td>Moderate</td>
<td>Yes, with spastic bladder</td>
<td>Hyperornithinaemia</td>
<td>Hypertymia, speech, distal axonal polyneuropathy</td>
<td>Pigmentary retinopathy, cataracts, macular thinning</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>(p.R138*)</td>
<td>Yes, with spastic bladder</td>
<td>Limb</td>
<td>Moderate axonal polyneuropathy</td>
<td>Limb, speech</td>
<td>Pigmentary retinopathy, cataracts, macular thinning</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>(p.R345*)</td>
<td>Yes, with spastic bladder</td>
<td>Limb</td>
<td>Moderate axonal polyneuropathy</td>
<td>Limb, speech</td>
<td>Pigmentary retinopathy, cataracts, macular thinning</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>(p.R345*)</td>
<td>Yes, with spastic bladder</td>
<td>Limb</td>
<td>Moderate axonal polyneuropathy</td>
<td>Limb, speech</td>
<td>Pigmentary retinopathy, cataracts, macular thinning</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>(p.R138*)</td>
<td>Yes, with spastic bladder</td>
<td>No</td>
<td></td>
<td>No</td>
<td></td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>(p.T167N)</td>
<td>No</td>
<td>No</td>
<td>Yes, with spastic bladder</td>
<td></td>
<td></td>
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</tbody>
</table>

**RESULTS Molecular genetics.** Whole exome sequencing identified a homozygous c.1752C>T (p.Q578*) nonsense mutation in AP5Z1 (hg19/GRCh37, NM_014855) in patient 1. Compound heterozygous nonsense mutations c.412C>T (p.R138*) and c.1033C>T (p.R345*) were identified by whole exome sequencing in patient 2 and confirmed by Sanger sequencing in patients 2, 3, and 4. A homozygous c.1364C>T (p.P455L) missense mutation in AP5Z1 was identified in patient 5, predicted to be deleterious and not observed in variant databases. Whole exome sequencing also disclosed compound heterozygous c.500C>A (p.T167N) and c.2010C>A (p.F670L) mutations in AP5Z1 in patient 6, predicted to be pathogenic (table). Both variants seen in patient 6 have been observed in the heterozygous form in the ExAc Browser data set among individuals of African descent (minor allele frequencies = 0.00004913 [p.T167N]; 0.00003360 [p.F670L]), while the nonsense variants have not previously been reported with the exception of the c.412C>T (p.R138*) variant.2 Mutations were confirmed by Sanger sequencing, and no other pathogenic or likely pathogenic changes in any other known HSP genes were detected. Immunoblotting confirmed a loss of protein in fibroblast cell lines derived from the nonsense mutations (figure e-1).

**Histology and electron microscopy.** We evaluated fibroblast lines from patients 1 and 5 for the presence of autofluorescent storage material and periodic acid Schiff (PAS)–positive staining by comparing them with age- and sex-matched controls. We detected
both autofluorescence and accentuated PAS staining in patient cell lines (figure 3) consistent with ceroid lipofuscin deposition. This led us to further characterize patient fibroblasts using transmission electron microscopy, which revealed consistent accumulation of aberrant multilamellar storage material in patient lines (figure 4). Further characterization revealed that these endocytic structures were positive for markers of endolysosomes, such as LAMP1 and CD63, and consistent with an AP5Z1-knockdown phenotype in HeLa cells.

**DISCUSSION** We present a series of patients with biallelic mutations in AP5Z1. We were able to confirm an ablation of AP-5 z protein by Western blot in patients 1, 2, and 4, each of whom harbored homozygous nonsense mutations (figure e-1). The c.412C>T (p.R138*) mutation in patients 2–4 of Belgian origin has been reported previously in a compound heterozygous patient of Italian origin. Protein levels of AP-5 z were unaffected by the missense variants seen in patients 5 and 6. Moreover, since the normal cellular function of AP-5 is not yet known, we were not able to perform functional assays to confirm the pathogenicity of the variants seen in patients 5 and 6. Conversely, patients 5 and 6 harbor ultra-rare variants at highly conserved residues, and cells from patient 5 show accumulation of multilamellar storage material, less prominent than in the nonsense cases but similar in appearance. Overall, we regard the c.1364C>T, c.500C>A, and c.2010C>A variants as suspected mutations but at this point are unable to confirm this unequivocally.

Mutations in all 4 subunits of another adaptor protein, AP-4, have been shown to lead to spastic paraplegia, highlighting the obligate nature of adaptor protein complex subunits. This raises the possibility that mutations in other AP-5 subunits may lead to a similar phenotype to that seen in AP5Z1. However, to date, no confirmed pathogenic mutations in AP5B1, AP5S1, or AP5M1 have been identified.

Most AP5Z1 patients in our series showed evidence of a leukoencephalopathy affecting the periventricular white matter, corona radiata, and centrum semiovale (figure 1A). In some cases, this led to an “ears of the lynx”-like appearance on brain MRI similar to that commonly seen in SPG11 and SPG15 patients (figure 1B). A thin corpus callosum is also a hallmark of patients with SPG11 and SPG15. Of interest, while not invariant, focal atrophy of the body of the corpus callosum was observed in several AP5Z1 patients, although not the more general thinning seen in SPG11 or SPG15 (figure 1D). A novel neuroimaging feature we also observed in our series was punctate T2 hyperintensities affecting the caudate, putamen, and thalamus with relative sparing of the globus pallidus, and putaminal rim hyperintensities were also noted in several patients (figure 1C).

Although prior reports identified prominent spasticity and ataxia in AP5Z1 patients, the patients in our series exhibited a diverse spectrum of movement disorders, including ataxia, myoclonus, spasticity, dystonia, and parkinsonism. The build-up of the abnormal storage material we observed in patient cells is likely to accumulate more focally in brain regions with high endogenous AP5Z1 expression, including the striatum, midbrain, and cerebellum (Allen Brain Atlas). We anticipate that this would lead to preferential degeneration of these select brain regions. Indeed, we observed neuroradiologic abnormalities of the striatum, midbrain,

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**Figure 3** Histologic findings in AP-5 patient fibroblasts

(A) Although light microscopic images of controls and patient cells appear similar, patient cells exhibit increased autofluorescence (B) and enhanced periodic acid-Schiff (PAS) uptake (C), indicating the presence of intracellular storage material.
and cerebellum which correlate with the phenotypic features we observed. Recent postmortem findings in SPG11 have shown widespread CNS degeneration, affecting cortical/subcortical regions, as well as basal ganglia, brainstem, and spinal cord; comparative postmortem studies in AP5Z1 patients may yield new insights into the cellular nature of these neuroimaging abnormalities.

Patient-derived fibroblasts from a number of AP5Z1 patient lines were fixed and processed for conventional electron microscopy. Note the accumulation of aberrant lamellar storage material in patient 1 (p.Q578*) homozygous fibroblasts compared with age-matched controls. For comparison, similar accumulations are seen in other nonsense AP5Z1 patients (p.R27Lfs*3, p [R138*]; [W441*]); the clinical features of these patients have been reported previously.1,2

Figure 4 Electron microscopic findings in AP-5 patient cells

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An animal model of SPG15 has identified abnormal endolysosomal processing and the accumulation of autofluorescent storage material in lysosomes, reminiscent of neuronal ceroid lipofuscinoses. Patient-derived fibroblasts from SPG11 and SPG15 patients also show accumulation of enlarged lysosomes similar to what we observe in AP5Z1 patients. Of interest, neuronopathic lysosomal storage disorders such as Gaucher disease and Niemann-Pick C may lead to parkinsonism, dystonia, and ataxia. Together, these findings suggest considerable overlap among these disorders.

Two AP5Z1 patients from the Belgian kindred showed evidence of midbrain atrophy with sparing of the pons (figure 1D), suggestive of a “hummingbird sign,” classically associated with progressive supranuclear palsy (PSP). PSP typically presents in late adulthood with gait impairment, parkinsonism, dementia, and impaired saccades, with supranuclear gaze palsy typically being a late finding. Similarly, we found that AP5Z1 patients may exhibit all of these features, although spasticity suggests an atypical form of PSP. Decreased outer and inner nerve fiber layer thickness by optical coherence tomography has been shown in patients with PSP, similar to that observed in our AP5Z1 cases. Rare cases have been linked to mutations in MAPT and triplet repeat expansions in ATXN2, although the vast majority of cases remain unexplained. It is intriguing when one recognizes that these 2 AP5Z1 cases share some features of PSP, and although a connection is speculative, it is perhaps worth further consideration in genetic studies of PSP.

This series of patients positive to AP5Z1 mutation demonstrates the phenotypic heterogeneity and wide age range at presentation that may be observed in affected individuals. Nevertheless, the combination of intellectual disability, sensorimotor neuropathy, hereditary spastic paraplegia, ataxia, and/or parkinsonism along with consistent findings on skin biopsy should suggest the possibility of AP5Z1 mutation. Further molecular analysis of complicated HSP cohorts will help determine the relative frequency of AP5Z1 mutations in this population, while detailed clinical characterization of additional patients will allow further genotype–phenotype analyses.

AUTHOR CONTRIBUTIONS

Dr. Hirx, Dr. Madeo, Dr. Smets, and Dr. Blackstone contributed to study concept and design, data acquisition, analysis and interpretation, and contributed to the critical revision of the manuscript for important intellectual content. Dr. Edgar, Dr. Schols, and Dr. Li contributed to data acquisition, analysis and interpretation, and contributed to the critical revision of the manuscript for important intellectual content. Ms. Yarrow, Ms. Deconinck, Dr. Baets, Dr. Van Aken, Dr. De Bloeker, Dr. Darles, Dr. Roda, Dr. Liepert, Dr. Mariotti, and Dr. De Jonghe contributed to data acquisition, analysis and interpretation. Dr. Zuchner contributed to study concept and design, data acquisition, analysis and interpretation. Dr. Krueger oversaw the project to completion, and contributed to study concept and design, data acquisition, analysis and interpretation, and contributed to the writing and critical revision of the manuscript for important intellectual content.

ACKNOWLEDGMENT

The authors thank the patients and their families for their participation in our research; without their gracious support none of these studies would have been possible.

STUDY FUNDING

This work was supported by a Doris Duke Clinical Scientist Development Award (2014112) (M.C.K.), a Shields Award (Child Neurology Foundation) (M.C.K.) and by a Dystonia Medical Research Foundation grant (M.C.K.). Portions of the work were supported by the Wellcome Trust (086598) to Margaret S. Robinson (J.H. and J.E.), by the Association Belgiquecontre les Maladies Neuromusculaires (ABMM) and the EU FP7/2007-2013 under grant agreement number 2012-305121 (NEUROMICS). Other portions of this work were supported by the German Research Council (DFG) grant SCH0754/3-2 (L.S.), the European Union grant F5-2013-305121 to NEUROMICS (L.S.), by the National Institutes of Neurological Disorders and Stroke (RO1NS066927) (to J.L.) and the National Center for Advancing Translational Sciences (UL1TR000445). J.B. has a Senior Clinical Researcher mandate of the Research Fund—Flanders (FWO). Portions of this research project were supported by NIH COBRE grants (P20 GM103620 and P20 GM103548) to Sanford Research. This work was also supported by the NIH Intramural Research Programs of the National Eye Institute (M.B.D.) and National Institutes of Neurological Disorders and Stroke (R.H.R., C.B.).

DISCLOSURE

Dr. Hirx has served on the editorial board of BMC Cell Biology, and has received research support from the Wellcome Trust. Dr. Madeo and Dr. Smets report no disclosures. Dr. Edgar has received research support from the Wellcome Trust. Dr. Schols has received research support from Santhera Pharmaceuticals, Genetic disorders in Arab Societies (grant SCHO754/5-2), miniMORPH (miniNET, grant 01GM0864), EUROSCAR (01GM1207), NEUROMICS (F5-2012-305121), the HSP-Selbsthilfegruppe Deutschland eV, and the Förderverein fuer HSP-Forschung. Dr. Li has served on the scientific advisory board of the Muscular Dystrophy Association and the Charcot-Marie-Tooth Association; and has served on the editorial boards of the Journal of the Peripheral Nervous System, Experimental Neurology, Neurology: Neuroimmunology & Neuroinflammation, and Neural Regeneration Research. Ms. Yarrow, Ms. DeConinck, Dr. Baerts, Dr. Van Aken, and Dr. De Bloeker report no disclosures. Dr. Darles has received research support from NIH and the Johns Hopkins University School of Medicine. Dr. Roda has received research support from NIH and the Johns Hopkins University. Dr. Liepert and Dr. Zuchner report no disclosures. Dr. Mariotti has received research support from the European Commission and the European Friedreich Ataxia Consortium for Translational Studies (EFACTS). Dr. De Jonghe has served on the editorial board of Acta Neurologica Belgica; and has received research support from the Fund for Scientific Research, International Coordination Action. Dr. Blackstone has served on the editorial boards of the Journal of Clinical Investigation, the Journal of Neurovascular Disease, and Annals of Neurology; has received research support from NIH/National Institutes of Neurological Disorders and Stroke; and has received license fee payments for monoclonal antibody against the human atlastin-1 protein, licensed to EMD Millipore Corporation. Dr. Krueger has served as a grant reviewer for the Department of Defense; has served as a scientific advisory committee member for Lundbeck, Inc.; has served on the speakers’ bureau of the Huntington Disease Society of America; has received research support from Retrosphin, NIH/National Institutes of Neurological Disorders and Stroke, and the Doris Duke Charitable Foundation; and has been involved with legal proceedings as a consultant for the HRSA National Vaccine Injury & Compensation Program. Go to Neurology.org/ng for full disclosure forms.

Received February 4, 2016. Accepted in final form July 6, 2016.
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Complicated spastic paraplegia in patients with AP5Z1 mutations (SPG48)
Jennifer Hirst, Marianna Madeo, Katrien Smets, et al.
Neurol Genet 2016;2;
DOI 10.1212/NXG.0000000000000098

This information is current as of August 25, 2016
CORRECTION
Complicated spastic paraplegia in patients with AP5Z1 mutations (SPG48)

In the article “Complicated spastic paraplegia in patients with AP5Z1 mutations (SPG48)” by J. Hirst et al.,1 there is an error in the second sentence of the introduction. The third subunit should read only “ζ” (zeta) rather than “ζζ” as originally published. The authors regret the error.

REFERENCE