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LETTER TO THE EDITOR

The blurred scenario of motor neuron disorders linked to *Spatacsin* mutations: a case report

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Complicated autosomal recessive hereditary spastic paraplegia (HSP) with thin corpus callosum (AR-HSP-TCC or SPG11; OMIM #604360) is characterized by early onset spasticity of the lower extremities and mental retardation [1]. Autosomal recessive juvenile amyotrophic lateral sclerosis (AR-JALS or ALS5; OMIM %602099 phenotype) is a rare form of hereditary amyotrophic lateral sclerosis (ALS) occurring before the age of 25 and clinically characterized by the involvement of upper (UMN) and lower (LMN) motor neurons [2]. Both AR-HSP-TCC and AR-JALS are caused by mutations in the *Spatacsin* gene [3,4]. We report the genetic and clinical analysis of a patient affected with sporadic motor neuron disease and carrying a compound heterozygous mutation in *Spatacsin*.

A 23-year-old woman was referred to our clinic for suspected ALS. She had achieved normal psychomotor milestones and, from the age of 17, she presented a progressive gait disorder mainly due to an increased stiffness in the lower limbs. Widespread LMN signs were also detected by electromyography (EMG). When she came to our attention she could only walk with bilateral support and needed the wheelchair for long distances.

At the last evaluation, 7 years later, she was wheelchair-bound with no bulbar or respiratory problems. The patient was unable to walk and to stand due to stiffness and muscle weakness (mean score 3/5 according to the Medical Research Council scale) in the lower limbs. She also showed a mild weakness (mean score 4/5) of the upper limb muscles. A severe amyotrophy was observed distally in the four limbs. Tone was increased in the legs and brisk reflexes along with bilateral extensor plantar response were detected. Sensory and cerebellar examinations yielded normal findings. Cranial nerves were spared.

The patient had a normal quotient of intelligence, evaluated by the Italian version of Nation Adult Reading Test, but showed a significant defect in memory-recall tests and in verbal phonemic fluency. The patient's family and past medical histories were unremarkable. Blood biochemistry and cerebrospinal fluid examination were normal.

EMG showed active and chronic denervation in all limb muscles. Nerve conduction studies were consistent with a mild mixed axonal and demyelinating sensorimotor peripheral neuropathy. Left quadriceps muscle biopsy confirmed a pattern of chronic neurogenic denervation (Fig. 1a). Motor evoked potentials

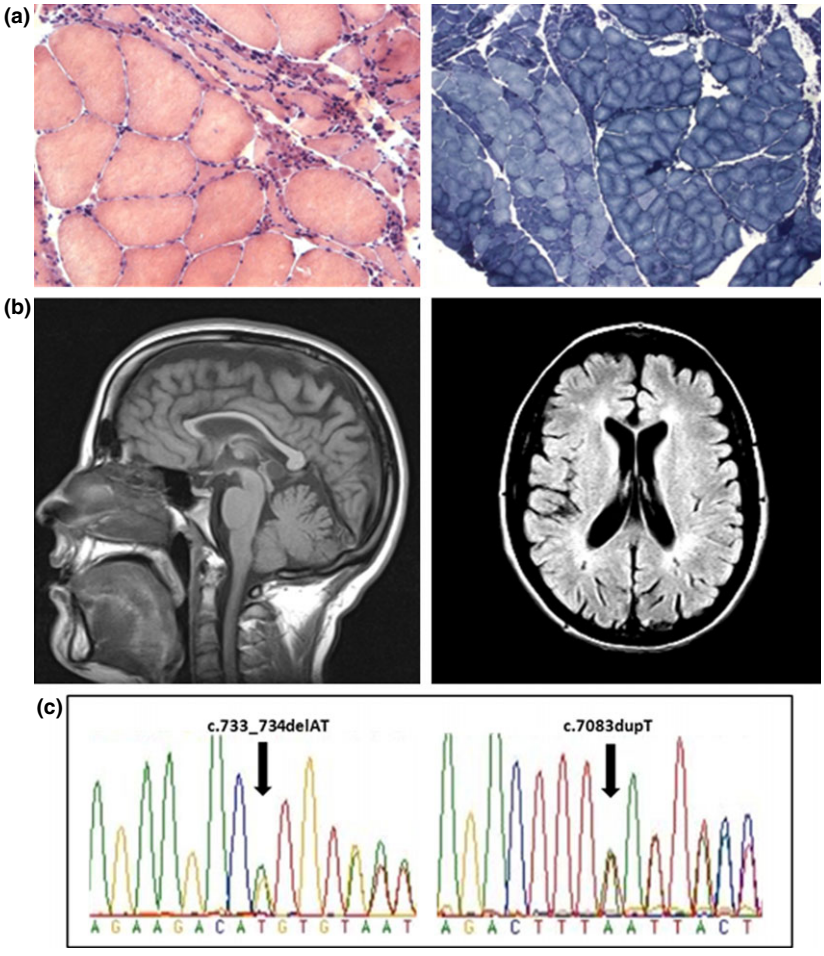

Figure 1 (a) Skeletal muscle pathology of the patient. Left panel, atrophic angulated fibers consistent with neurogenic atrophy (H&E, 100×); right panel, fiber type grouping indicating a reinnervation process (NADH-TR, 25×). (b) MRI findings. Left panel, thinning of corpus callosum; right panel, diffuse white matter abnormalities on the patient's MRI image. (c) Sanger sequence of mutations identified. Left panel, c.733_734delAT (chr15:44949428-44949428 on GRh37_hg19); right panel, c.7083dupT (chr15:44856813 on GRh37_hg19).

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of the four extremities pointed to an increased central conduction time.

Brain magnetic resonance imaging (MRI) showed diffuse white matter abnormalities. A slight thinning of the corpus callosum was also reported (Fig. 1b). Spinal cord MRI was normal.

A diagnosis of complicated spastic paraplegia was made. Direct sequencing of *Spatacsin* identified two heterozygous mutations: p.Met245Valfs*1 and p.Asn2362Stopfs (c.733_734delAT and c.7083dupT respectively, reference sequence NM_025137). Whilst the former has already been reported in association with AR-HSP-TCC [1], the latter is novel and is not found in public databases.

Even though a diagnosis of AR-HSP-TCC was made, some clinical findings could suggest an ALS phenotype. First, widespread signs of LMN involvement, probably unrelated to the mild coexistent neuropathy, were detected clinically and instrumentally. Secondly, our patient demonstrated frontal lobe dysfunctions typical of ALS and no mental retardation. Thirdly, this patient matched El Escorial revisited criteria for definite ALS, i.e. UMN and LMN signs in at least three motor neuron regions [5], and was referred to our center because of a suspected ALS. Finally, disease progression was consistent with both AR-HSP-TCC and AR-JALS. Unlike typical ALS, AR-JALS is indeed characterized by a slowly progressive dysfunction of UMN and LMN with a mean disease duration of about 34 years [2].

A wide clinical heterogeneity has been observed for both spastic paraplegia [3] and ALS due to *Spatacsin* mutations. Daoud *et al*. [6] reported two ALS familiar cases, carrying identical an *Spatacsin* mutation, showing different clinical pictures. Notably, one of these had a classical presentation of autosomal recessive HSP with corpus callosum atrophy. It thus appears that the lines between ALS and HSP phenotypes due to *Spatacsin* mutations are blurred. Nonetheless, an overlap between HSP, ALS and other motor neuron diseases has already been reported for other genes [7–9].

This study demonstrates that loss of *Spatacsin* can result in an overlapping phenotype exhibiting features of ALS and spastic paraplegia. Whilst widening the genetic spectrum of *Spatacsin* mutations, this report highlights the complexity of a correct clinical categorization of motor neuron diseases linked to *Spatacsin*.

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Disclosure of conflicts of interest

The authors declare no financial or other conflicts of interest.

References

1. Stevanin G, Azzedine H, Denora P, *et al.* Mutations in SPG11 are frequent in autosomal recessive spastic paraplegia with thin corpus callosum, cognitive decline and lower motor neuron degeneration. *Brain* 2008; **131:** 772–784.
2. Orlacchio A, Babalini C, Borreca A, *et al.* SPATACSIN mutation cause autosomal recessive juvenile amyotrophic lateral sclerosis. *Brain* 2010; **133:** 591–598.
3. Paisan-Ruiza C, Nathb P, Wooda NW, *et al.* Clinical heterogeneity and genotype–phenotype correlations in hereditary spastic paraplegia because of Spatacsin mutations (SPG11). *Eur J Neurol* 2008; **15:** 1065–1070.
4. Renton AE, Chiò A, Traynor BJ. State of play in amyotrophic lateral sclerosis genetics. *Nat Neurosci* 2014; **17:** 17–23.
5. Brooks BR, Miller RG, Swash M, *et al.* El Escorial revisited: revised criteria for the diagnosis of amyotrophic lateral sclerosis. *Amyotroph Lateral Scler Other Motor Neuron Disord* 2000; **1:** 293–299.
6. Daoud H, Zhou S, Noreau A, *et al.* Exome sequencing reveals SPG11 mutations causing juvenile ALS. *Neurobiol Aging* 2012; **33:** 839.
7. Al-Saif A, Bohlega S, Al-Mohanna F. Loss of ERLIN2 function leads to juvenile primary lateral sclerosis. *Ann Neurol* 2012; **72:** 510–516.
8. Wakil SM, Ramzan K, Abuthuraya R, *et al.* Infantile-onset ascending hereditary spastic paraplegia with bulbar involvement due to the novel ALS2 mutation c.2761C>T. *Gene* 2014; **536:** 217–220.
9. Vengoechea J, David MP, Yaghi SR, Carpenter L, Rudnicki SA. Clinical variability and female penetrance in X-linked familial FTD/ALS caused by a P506S mutation in UBQLN2. *Amyotroph Lateral Scler Other Motor Neuron Disord* 2013; **14:** 615–619.

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