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LETTER TO THE EDITOR

Seipin/BSCL2 mutation screening in sporadic adult-onset upper motor neuron syndromes

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Sirs,

The ability to distinguish between sporadic presentations of hereditary spastic paraparesis (HSP) and primary lateral sclerosis (PLS) is important in terms of prognostication and genetic counseling, but clinical differentiation is problematic [6]. Primary lateral scherosis is a sporadic disorder of progressive spino-bulbar spasticity and may be part of the clinical spectrum of amyotrophic lateral sclerosis (ALS) [10]. Hereditary spastic paraparesis is a clinically and genetically heterogeneous group of disorders characterized by a slowly progressive spastic paraparesis [8, 12].

To date, 15 genes and more than 20 additional loci have been identified for autosomal dominant (AD), autosomal recessive and X-linked forms of HSP [5, 7]. The *spastin* gene (SPG4) mutation is the most frequent cause of AD HSP (around 40% of families) and is also frequent in sporadic HSP (13%), but not in PLS [3]. We recently found pathogenic *paraplegin* gene (SPG7) mutations 11% of patients with sporadic HSP [4]. The role of other HSP genes in sporadic upper motor neuron (UMN) syndromes is largely unknown. Two known mutations (c.263G>A/p.N88S and c.269C>T/p.S90L) in exon 3 of the *seipin/BSCL2* gene (SPG17) can cause a range of AD (mixed) upper and lower motor neuron disorders, including Silver syndrome (HSP with amyotrophy of the hands), variants of Charcot–Marie-tooth disease type 2, distal hereditary motor neuropathy type V (dHMNV), but also pure and complicated forms of HSP [1, 13, 14]. Because of incomplete penetrance, the *seipin/BSCL2* mutation can manifest as a sporadic disease [14].

To investigate whether these two *seipin/BSCL2* mutations are present in patients with sporadic HSP and PLS, we screened exon 3 of the *seipin/BSCL2* gene in 86 Dutch patients with a sporadic adult-onset UMN syndrome. Inclusion criteria were a gradually progressive UMN syndrome, adult-onset, disease duration >6 months and a negative family history. Exclusion criteria were lower motor neuron loss meeting the revised El Escorial criteria for clinically definite, clinically probable or probable laboratory-supported ALS [2] and evidence of other causes of a UMN syndrome based on a battery of laboratory investigations, including serum biochemistry (including thyroid-stimulating hormone, angiotensin converting enzyme, vitamin B12, folate and vitamin E), analysis of very long chain fatty acids in plasma, serology (syphilis, borreliosis, human T cell lymphotrophic virus type 1 and human immunodeficiency virus) and bile alcohol analysis in urine, and cerebral and spinal magnetic resonance imaging (MRI). The presence of the *SPG4* and *SPG7* mutations was excluded in all patients. The study was approved by the medical ethics review board of the University Medical Center in Utrecht, and written informed consent was obtained from all patients.

Mutation screening of the *seipin/BSCL2* gene was performed using automated forward and reverse direct sequencing of exon 3. The *BSCL2* exon 3 was amplified by PCR using intronic primers (primer sequences available on request), and the PCR products were loaded on an Applied

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Biosystems 3730 DNA Analyzer (Applied Biosystems, Foster City, CA). Sequence data were analyzed using Phred-PolyPhred software (CodonCode, Dedham, WA) and compared to the *BSCL2* reference sequence (GenBank accession number NM_032667).

Clinical characteristics of the 86 included patients are shown in Table 1. No exon 3 mutations were detected. A previously reported, non-pathogenic polymorphism (c.294+11 G>T) [11] was identified in 27 patients (Table 2). This allele frequency is consistent with a previous report [11] and with our own data (minor allele frequency of c.294+11 G>T of 0.20 in 50 unrelated reference samples from unaffected individuals).

We did not search for *seipin/BSCL2* mutations outside of exon 3. Results from previous studies, however, suggest that the c.263G>A (p.N88S) and c.269C>T (p.S90L) mutations in exon 3 are probably the only two *seipin/BSCL2* mutations associated with Silver syndrome and distal hereditary motor neuropathy type V and that, therefore, *seipin/BSCL2* mutation analysis for these disorders may be restricted to exon 3 [11]. Both of these exon 3 mutations destroy a predicted *N*-glycosylation site of the seipin protein, which probably causes the accumulation of the misfolded mutant seipin in the endoplasmic reticulum (ER), leading to cell death as a result of ER stress [9].

Our population included 40 patients with a phenotype of spastic paraparesis similar to pure HSP. In families with the *seipin/BSCL2* mutation, the frequency of an HSP phenotype has been observed to be as high as 10% of patients [1]. The other 46 patients in our study had symptomatic UMN involvement of the arms or bulbar region, which may suggest a diagnosis of PLS [6, 10]. The results of our study indicate that the *seipin/BSCL2* exon 3 mutations are not a common cause of sporadic pure HSP and PLS. Therefore, they do not support inclusion of the *Seipin/BSCL2* gene in the group of first-choice HSP genes to screen for mutations during the diagnostic work-up of sporadic HSP and PLS.

Table 1 Characteristics of the 86 patients of our study with a sporadic adult-onset upper motor neuron syndrome

Sex, *n* (%)	
Male	56 (65)
Female	30 (35)
Age at onset, years, median (range)	51 (18–77)
Disease duration, years, median (range)	6 (1–29)
Site of onset, *n* (%)	
Bulbar region	7 (8)
Arms	3 (3)
Legs	76 (88)
Affected body regions, *n* (%)	
Bulbar and spinal	32 (37)
Arms and legs	14 (16)
Legs only	40 (47)
Needle EMG	
Number of patients studied (*n*)	69
Abnormal, *n* (%)	37 (54)

EMG, Electromyography; *abnormal*, mild signs of active or chronic denervation (not fulfilling El Escorial criteria for amyotrophic lateral sclerosis [2])

Table 2 Frequency of the *seipin/BSCL2* exon 3 polymorphism in 86 patients with a sporadic adult-onset upper motor neuron syndrome

Polymorphism	Number of patients
c.294+11 G>T	27
Heterozygous	25
Homozygous	2

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