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LETTER TO THE EDITOR

Multisystemic *SYNE1* ataxia: confirming the high frequency and extending the mutational and phenotypic spectrum

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Sir,

We recently reported in *Brain* a large multi-centre study suggesting that truncating *SYNE1* mutations are a recurrent cause of recessive ataxia also outside Quebec (23/434 = 5.3% of patients with unexplained early-onset ataxia) (Synofzik *et al.*, 2016). Moreover, this study indicated that *SYNE1* ataxia might commonly present with complex multisystemic phenotypes rather than pure cerebellar ataxia, including in particular motor neuron and brainstem dysfunction (Synofzik *et al.*, 2016). However, confirmation of both the frequency estimate and the complex phenotypic spectrum is still lacking, raising the question whether these findings indeed represent systematic results rather than just exceptional or coincidental associations.

Here, we now report the mutational and phenotypic findings on *SYNE1* from a second, independent ataxia series of 116 patients. These findings not only confirm the high frequency of SYNE1 ataxia and extend both the mutational spectrum (seven novel index patients, 12 novel *SYNE1* mutations) and the multisystemic phenotypic spectrum, including amyotrophic lateral sclerosis (ALS)-like motor neuron features, they also indicate that muscle immunohistochemistry might provide a valuable diagnostic biomarker for

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clarifying the pathogenic contribution of *SYNE1* missense variants. This observation may have consequences for clinical *SYNE1* diagnostics, as diagnostic tests are urgently needed for clarifying the role of the ubiquitous *SYNE1* missense variants with unknown clinical significance (VUS), which are frequently found in neurological and non-neurological patients and controls (Synofzik *et al.*, 2016).

Index subjects ($n = 116$) with unexplained degenerative ataxia compatible with autosomal recessive inheritance (no ataxia in the parental generation) and negative for trinucleotide repeat expansions causing Friedreich's ataxia (FRDA) were compiled from three sources: the Early Onset Ataxia Consortium ($n = 88$), the ataxia centre Antwerp, Belgium ($n = 9$), and the ataxia centre Milano, Italy ($n = 19$). All subjects originated from European, Middle East or Mediterranean countries. This series was sequenced after and independent from the cohort of the previous *SYNE1* study (Synofzik *et al.*, 2016). None of the subjects had been part of the previous screening cohort. Subjects were screened for *SYNE1* mutations by one of the following three next-generation sequencing methods: (i) a high coverage HaloPlex gene panel kit (Agilent) including >120 known ataxia genes ($n = 88$); (ii) targeted exon-capture sequencing strategy (Illumina Nextera Rapid Capture Custom kit) including 107 known ataxia genes ($n = 19$); or (iii) whole-exome sequencing using the SureSelect Human All Exon 50 Mb kit (Agilent) ($n = 9$) (for technical details, filter settings, and criteria for inclusion of *SYNE1* missense variants, see the online Supplementary material). All index patients carrying two pathogenic *SYNE1* alleles and their affected siblings received a systematic clinical assessment, as described in detail in the previous study (Synofzik *et al.*, 2016) (Table 1).

We identified six index patients carrying two truncating *SYNE1* alleles and one index patient carrying one truncating plus one missense *SYNE1* allele, thus yielding a total of seven index patients out of 116 in the total ataxia cohort (6%). In these seven index patients, we observed a total of 12 different mutations, consisting of seven frameshift, three nonsense, one splice site, and one missense mutation in the actin binding domain (Table 2 and Fig. 1A). All 12 mutations, each confirmed by Sanger sequencing, have not yet been reported in association with human disease. For all families where DNA of at least one parent was available (5/7 families), we were able to show that the respective parent carried only one of the two corresponding *SYNE1* variants, supporting a biallelic localization of the variants in the index child. In one of the remaining two families, consanguinity was also suggestive of a biallelic location of the observed homozygous mutations.

The missense variant c.4732C>T; p.P1578S (observed in Patient 2-1) (i) segregated in *trans* with the frameshift deletion c.23767_23768delCA; p.Q7923Efs*4; (ii) had a very low minor allele frequency in ExAc (2.26E-04) and EVS6500 (7.70E-05); (iii) predicted to be damaging by three out of three *in silico* algorithms (Mutation Taster) (Schwarz *et al.*, 2010; Wang *et al.*, 2010); PolyPhen-2 HDIV (Adzhubei *et al.*, 2010), and Likelihood Ratio Test (LRT) (Chun and Fay, 2009); (iv) highly evolutionary conserved with scores PhyloP 100way = 6.03 and PhastCons 100way = 1.0 (Pollard *et al.*, 2010); and (v) ranked among the top 1% of all 8.6 billion single nucleotide variants in the GRCh37/hg19 (CADD score: 24.2) (Kircher *et al.*, 2014). However, given that even rare, well-conserved missense *SYNE1* variants have been shown to present a ubiquitous finding in control subjects (Synofzik *et al.*, 2016), additional functional evidence is needed to demonstrate a pathogenic contribution. Immunohistochemistry assessment of muscle tissue in Patient 2-1 showed severely reduced SYNE1 staining (Fig. 1B; for methodological details see Supplementary material), in line with the findings seen in patients with two truncating *SYNE1* mutations (Synofzik *et al.*, 2016). This suggests that the p.P1578S missense mutation, in combination with another truncating *SYNE1* variant, leads to loss of SYNE1 protein.

Clinical data were available for all eight affected subjects belonging to the seven index families. Age of disease onset was variable, ranging from 6 to 42 years (median onset: 14 years). Disease started in 4/8 patients (50%) with non-ataxia features, namely facial muscle fasciculations, speech disturbances, spasticity and cognitive deficits, respectively. At last examination (median age: 35 years), all 8/8 patients showed a 'cerebellar ataxia plus' phenotype, i.e. none of them showed the classical *SYNE1* phenotype of pure cerebellar ataxia. Seven of eight subjects (88%) exhibited ataxia plus motor neuron disease, which involved both upper motor neuron dysfunction (bilateral positive extensor plantar reflex and/or spasticity) and lower motor neuron dysfunction muscle atrophy, including bulbar muscles (Fig. 1C) combined with reduced reflexes; fasciculations clinically or on EMG; acute denervation in EMG] in 5/8 patients (63%), and only upper motor dysfunction in 2/8 patients (25%). In 2/8 patients (one also with motor neuron disease), ataxia was complicated by additional moderate-to-severe cognitive impairment across manifold neuropsychological domains, affecting in particular processing speed, attention, memory, and executive functions (for detailed neuropsychological test results of Patient 4-1, see Supplementary material). One index patient (Patient 2-1) showed a severe and complex multisystemic phenotype, comprising of very early onset (6 years of age) ataxia, upper and lower motor neuron damage, including acute neurogenic changes with creatine kinase elevation, and unilateral diaphragm paralysis with restrictive lung function. This finding confirms that the complex early-onset phenotypes reported in three subjects in the previous report (Synofzik *et al.*, 2016) are a recurrent manifestation of *SYNE1* disease.

These findings provide evidence from an independent, second series that SYNE1 deficiency is indeed a relatively common cause of non-FRDA recessive ataxia also outside Quebec, with a frequency of 5% (Synofzik *et al.*, 2016) to 6% (this report). Moreover, these findings further extend

Table 1 Clinical, imaging and electrophysiological features of SYNE1 patients

Patient ID	Phenotype category	Genotype (cDNA)	Origin/ gender	SARA score	SDFS	Age of onset	First clinical symptom	Age at last examination (years)	Cerebellar ataxia	Dysfunction upper motor neuron	Dysfunction lower motor neuron	Additional clinical features	Cerebellar atrophy (MRI)	Peripheral neuropathy (NCS)	EMG changes (muscle)	Abnormal MEPs
1-1	Ataxia MND	c.18583C>T; c.18583C>T;	Turkey/m	10	2	17	Fasciculations face	25	+; onset 20 yrs	+ signs; no spasticity	Fasciculations face		+	n	Anterior tibial and deltoid muscle: acute and chronic denervation	Prolonged UL + LL
1-2	Ataxia MND	c.18583C > T; c.18583C > T;	Turkey/m	23	3	11	Speech disturbance	28	+; onset 17 yrs	+ signs; no spasticity	+ thenar and hypothenar atrophy; fibrillation tongue	CK elevation (257U/l), pes equinovarus,	+	Tibial CMAP amplitude reduced	Anterior tibial and deltoid muscle: acute and chronic denervation	Prolonged UL + LL
2-1	Ataxia MND	c.23554_23555delCA; c.4732C > T	Belgium/f	14	5	6	Mild spasticity LL	28	+; onset 15yrs	+ signs; no spasticity	+ thenar atrophy (4-/5), mainly proximal in LL (4/5)	Unilateral diaphragm paralysis left with restrictive lung function, CK elevation (341 U/L),	n (age 22 years)	Reduced CMAP amplitudes LL; normal SNAP	Chronic denervation proximal and distal PSW, fibrillation potentials	n.d.
3-1	Ataxia MND	c.24814C > T c.13567_13570delGAAG	Turkey/f	19	6	28	Gait disturbance	37	+; onset 28yrs	+ signs; mild spasticity	-	Downbeat nystagmus	+	n	n	Normal UL, LL
4-1	Ataxia cognition	c.15029_15032delAGGA; c.15438 + 2T > A	Germany/f	14.5	4	42	Gait disturbance	49	+; onset 42yrs	-	-	Cognitive impairment: attention, memory, executive function	+	n	n	Normal UL, LL
5-1	Ataxia MND	c.10379_10380delAT; c.10996_ 11003delCTGGACGA	Germany/m	13	3	23	Gait disturbance	44	+; onset 23yrs	+ spasticity	fasciculations and atrophy tongue	Writer's cramp, polyneuropathy	+	Reduced sural SNAP and SNCV, normal tibial NCS	n.d.	n.d.
6-1	Ataxia MND cognition	c.1903dupA; c.1903dupA	Italy/m	9,5	2	7	Cognitive deficits; gait disturbance	35	+; onset 7 yrs	+ signs; spasticity	-	Cognitive impairment: attention, memory, executive function; impaired colour vision; urinary dysfunction; depression	+	n.d.	n.d.	n
7-1	Ataxia MND	c.25655delG; c.21971C > A	Italy/m	20	3	6	Speech and gait disturbance	27	+; onset 6 yrs	+ signs; spasticity	distal atrophy UL and LL	Hammer-toes, motor polyneuropathy	+	Reduced CMAP, normal, SNAP	Acute denervation LL and UL	n.d.

Patient ID = family number_individual number; ataxia MND = cerebellar ataxia plus motor neuron disease involving upper and/or lower neuron damage; m = male; f = female; + = present; - = absent; SARA = scale for the assessment and rating of ataxia; SDFS = spinocerebellar degeneration functional score, assessing disability stage from 1 to 7 (0: no functional handicap; 1: no functional handicap but signs at examination; 2: mild, able to run, walking unlimited; 3: moderate, unable to run, limited walking without help; 4: severe, walking with one stick; 5: walking with two sticks; 6: unable to walk, requiring wheelchair; 7: confined to the bed); upper motor neuron signs = extensor plantar response positive and/or hyperreflexia of muscle tendon reflexes; UL = upper limb, LL = lower limb; CK = creatine kinase; NCS = nerve conduction studies; CMAP = compound muscle action potential; SNAP = sensory nerve action potential; SNCV = sensory nerve conduction velocity; EMG = electromyography; MEP = motor evoked potentials; PSW = positive sharp waves; n.d. = not done; n = normal.

Table 2 SYNE1 mutations identified in this study

Variant ID	Family ID	Phenotype	Genomic variant	cDNA variant	Protein change	Variant type	Zygosity	PhyloP	CADD score	MAF 1000 genomes	MAF ExAC	MAF EVS6500	in HGMD
1	#1	Ataxia MND	chr6:152590412G > A	c.18583C > T	p.Q6195*	Stopgain SNV	Homo	8.90	56	0	0	0	absent
2	#2	Ataxia MND	chr6:152485320_152485321delTG	c.23767_23768delCA	p.Q7923Efs*4	Frameshift deletion	Het	NA	43	0	0	0	absent
3	#2	Ataxia MND	chr6:152751303G > A	c.4732C > T	p.P1578S	Missense	Het	6.03	24.2	0	2.26×10^{-4}	7.70×10^{-5}	absent
4	#3	Ataxia MND	chr6:152469342G > A	c.24814C > T	p.R8272*	Stopgain SNV	Het	1.93	53	0	8.25×10^{-6}	0	absent
5	#3	Ataxia MND	chr6:152652250_152652253delCTTC	c.13567_13570delGAAG	p.E4523Sfs*34	Frameshift	Het	NA	35	0	0	0	absent
6	#4	Ataxia cognition	chr6:152647692_152647695delTCCT	c.15029_15032delAGGA	p.E5010Vfs*13	Frameshift	Het	NA	37	0	0	0	absent
7	#4	Ataxia cognition	chr6:152647091A > T	c.15438 + 2T > A	?	Splice donor	Het	5.79	24.1	0	0	0	absent
8	#5	Ataxia MND	chr6:152680513_152680514delAT	c.10379_10380delAT	p.Y3460Cfs*28	Frameshift	Het	NA	36	0	0	0	absent
9	#5	Ataxia MND	chr6:152674803_152674810del TCGTCCAG	c.10996_11003delCT GGACGA	p.L3666Efs*51	Frameshift	Het	NA	37	0	0	0	absent
10	#6	Ataxia MND	chr6:152786422dup	c.1903dupA	p.M635Nfs*35	Frameshift	Homo	NA	33	0	0	0	absent
11	#7	Ataxia MND	chr6:152457757delC	c.25655delG	p.C8552Sfs*7	Frameshift	Het	NA	46	0	0	0	absent
12	#7	Ataxia MND	chr6:152540211G > T	c.21971C > A	p.S7324*	Stopgain SNV	Het	7.44	59	0	8.24×10^{-6}	0	absent

Genomic positions of the variants according to genome build hg19.

DNA changes according to NM_182961.3. Variant type and protein changes according to GVS function based on NP_149062. MND = motor neuron disease; zygosity = homozygous (homo) or heterozygous (het); PhyloP = PhyloP conservation score based on base-wise conservation across 100 vertebrates; CADD score = scaled Combined Annotation Dependent Depletion score, integrating many diverse annotations into a single measure (C score) for each variant. The predicted pathogenicity of each variant is scored and ranked relative to all ~8.6 billion single nucleotide variants of the GRCh37/hg19 reference. A scaled CADD score of 20 indicates variants at the top 1%, a CADD score of 30 indicates variants at the top 0.1%, etc. (Kircher *et al.*, 2014). MAF = minor allele frequency; ExAC = Exome Aggregation Consortium; EVS = Exome Variant Server 6500 exomes all from the NHLBI GO Exome Sequencing Project; HGMD = Human Gene Mutation Database; NA= not available.

the mutational spectrum of *SYNE1* disease by 12 novel mutations spread throughout the gene (yet sparing the KASH-domain, Fig. 1A), demonstrating the need to sequence not only particular 'hot spot' regions, but indeed the whole giant 146-exon gene.

These findings also help to explicate the multisystemic spectrum and disease course of *SYNE1* disease. They show that multisystemic ataxia plus syndromes are not the exception, but the rule, with up to 100% of SYNE1 patients outside Canada presenting with ataxia plus syndromes, in particular complicated by upper and/or lower motor neuron disease. In up to 50% of patients, *SYNE1* disease even starts with non-cerebellar features. The combination of upper plus lower motor neuron disease (seen in 63% of patients), which can include fasciculations, acute denervation and damage of bulbar motor neurons (see tongue atrophy, Fig. 1C), resembles ALS-like motor neuron features. Our findings demonstrate that such complex early-onset syndromes with upper and lower motor neuron disease and respiratory features are not a coincidental finding, but a recurrent manifestation of truncating *SYNE1* mutations (Izumi *et al.*, 2013; Synofzik *et al.*, 2016). This contrasts the view on *SYNE1* ataxia as relatively benign, slowly progressive ataxia, which was largely traced from French-Canadian *SYNE1* patients (Dupre *et al.*, 1993/2012, 2007).

Determining the pathogenicity of *SYNE1* missense mutations will present a complex challenge in future clinical diagnostics, given that even rare, well conserved missense variants can be found in 5.6% of controls with unrelated disease conditions or phenotypes (Synofzik *et al.*, 2016). Here we show that SYNE1 muscle staining might help to show a loss of SYNE1 protein in subjects carrying a *SYNE1* missense variant. Muscle immunohistochemistry would thus help to corroborate the pathogenicity of at least some well selected, rare, highly conserved *SYNE1* missense variants, in particular if located in *trans* with another truncating variant.

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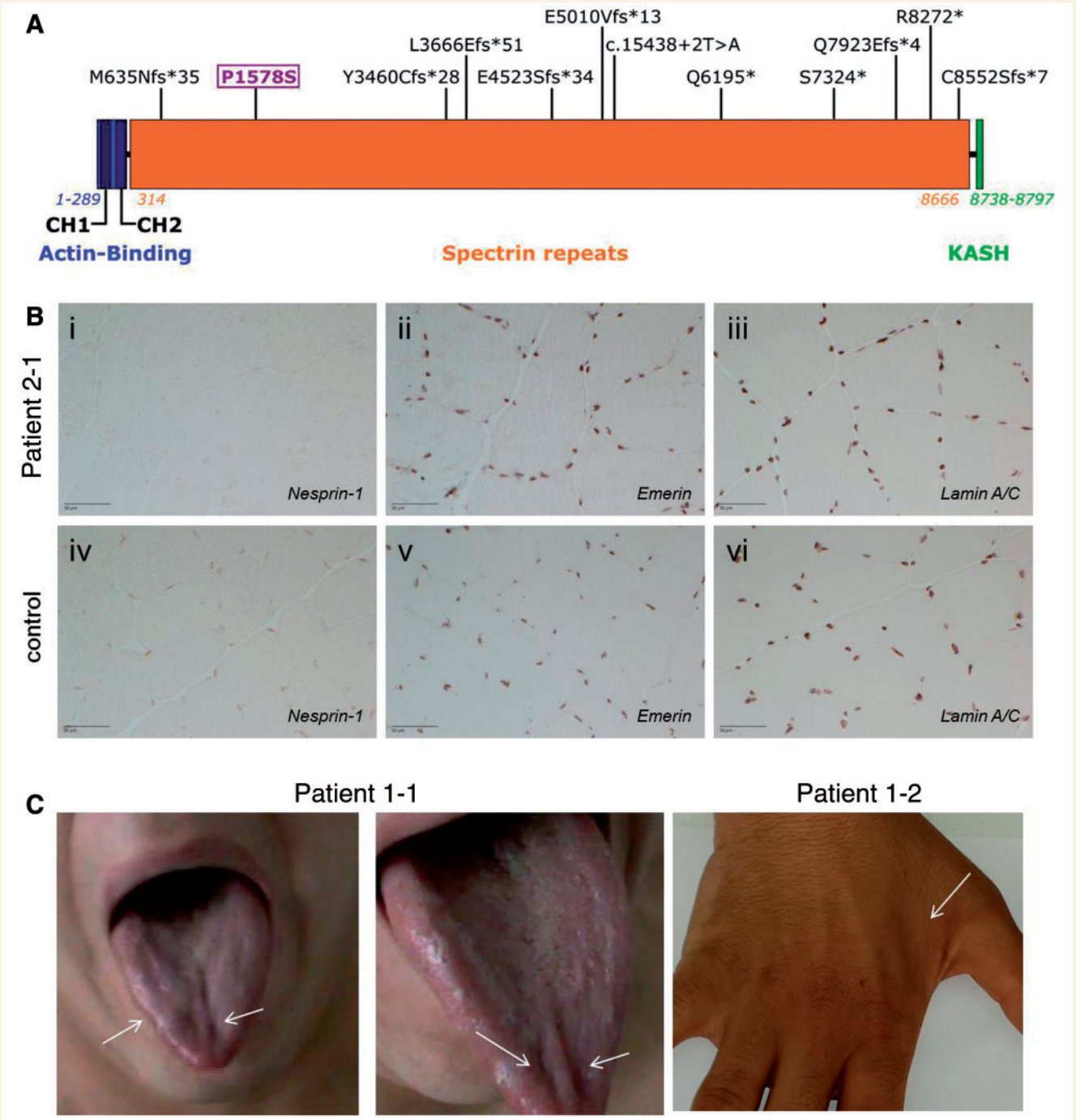

Figure 1 Mutational spectrum, muscle immunolabelling, and atrophy findings in SYNE1 patients. (**A**) Graphical overview of the mutations found in this study in relation to the SYNE1 domains. The mutations identified in this study are indicated at their respective position in the *SYNE1* gene. The N-terminal actin-binding domain (in blue) contains two calponin homology domains (CH1 and CH2); spectrin repeats (orange) contain all the mutations detected in this study; the C-terminal KASH domain (Klarsicht/ANC-1/Syne homology domain) is coloured in green. The missense variant investigated in this study is marked in purple. (**B**) Absent SYNE1 staining in muscle tissue in a patient carrying a missense plus a truncating *SYNE1* mutation. After immunolabelling of nesprin-1, staining of the nuclear envelope was absent in Patient 2-1 carrying a missense (c.4732C > T; p.P1578S) plus a truncating *SYNE1* mutation (**i**), but present in quadriceps muscle of a healthy control (**iv**) (peroxidase-antiperoxidase technique). Immunolabelling of emerin and lamin A/C at the inner nuclear membrane were normal in patient and control (ii/iii and v/vi, respectively) (avidin-biotin complex technique), thus ruling out an unspecific lack of staining in this subject. Scale bar = 50 μm. (**C**) Tongue and interosseous muscle atrophy illustrating lower motor neuron degeneration in *SYNE1* disease. Photographs of the tongue of Patient 1-1 (*left*) and of the hand of Patient 1-2 (*right*) illustrating atrophy of the right lateral and medial tongue and of the first dorsal interosseous muscle, respectively, illustrating affection of bulbar and cervical motor neurons in SYNE1 disease. The tongue also showed generalized fasciculations (not seen on the static photographic image).

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Supplementary material

Supplementary material is available at *Brain* online.

Appendix 1

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