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Short communication

SYNE1-ataxia: Novel genotypic and phenotypic findings

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ABSTRACT

Introduction: *SYNE1* encodes nesprin-1, a scaffold protein which is involved in the binding between cytoskeleton, nuclear envelope and other subcellular compartments. In 2007, recessive truncating *SYNE1* mutations have been linked to a genetic form of pure cerebellar ataxia with adult onset and mild phenotype. Subsequent reports described a number of patients with *SYNE1*-ataxia and widespread neurological involvement including features of motor neuron disease. Recently, heterozygote missense *SYNE1* mutations have been associated with muscular disorders, such as Emery-Dreifuss muscular dystrophy, arthrogryposis multiplex congenita and dilated cardiomyopathy.

Methods: Herein we describe novel genotypic and phenotypic findings in an independent cohort of 5 patients with *SYNE1*-ataxia referring to the Department of Neurology of the Innsbruck Medical University and performed a review of the related literature.

Results: We report 3 novel mutations and describe for the first time myocardial involvement in a patient with a complicated spastic-ataxic phenotype and C-terminal mutation. In the literature, mutations associated with additional motor neuron signs spanned over the entire gene, but patients with a particularly severe phenotype and premature death bore C-terminal mutations.

Conclusion: Our findings support a genotype-phenotype correlation in *SYNE1*-ataxia and suggest the need for a systematic cardiologic evaluation in the setting of complicated spastic-ataxia phenotypes.

1. Introduction

SYNE1 is an exceptionally large human gene encoding the protein nesprin-1 [1]. Nesprins are a family of intracellular scaffold proteins which mediate anchoring between nuclear envelope, other subcellular compartments and the cytoskeleton [1]. Nesprins bind cytoskeletal actin via a calponin-domain at the N-terminus and the nuclear envelope via a KASH domain at the C-terminus. The central part of the protein consists of a variable number of spectrin-domains, which probably mediate anchoring and interaction with other intracellular proteins and organelles [2].

In 2007 truncating recessive *SYNE1* mutations were identified in a cluster of French Canadian families with adult onset pure cerebellar ataxia for the first time [3,4]. This newly recognized condition was defined as autosomal recessive cerebellar ataxia type 1 (ARCA1) and subsequently described in other ethnicities [5–10]. ARCA1 was initially believed to result in a relatively mild phenotype, with isolated cerebellar ataxia, but up to now around 30 patients have been reported, who displayed a complex phenotype with more widespread neurologic and non-neurologic dysfunction [5,8,11,12]. In most cases additional neurological features consisted of upper and lower motor neuron involvement in various combinations, ranging from a spastic-ataxic gait to early onset amyotrophy, paresis and respiratory distress [12].

In the present paper, we describe the clinical features in a cohort of newly identified patients with *SYNE1*-ataxia examined at a third referral center in Austria and provide a review of the related literature.

1.1. Patients and methods

Six patients from 3 unrelated families were referred to the Department of Neurology of Innsbruck Medical University because of the clinical finding of a cerebellar syndrome with likely recessive

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inheritance (healthy parents, disease in more than 1 sibling). Five patients agreed to undergo genetic testing and provided written informed consent. In the present manuscript, roman numerals identify families and Arabic numerals individuals.

In patients III-1 and III-2, genetic testing was performed in our Division of Human Genetics by linkage analysis using a DNA-SNP-array (CytoSNP12v2.1 chip Illumina), and subsequent massive parallel sequencing of potential candidate genes by exome analysis. In the other patients genetic testing was performed in a certified external laboratory (Centogene, Rostock) by means of a panel for autosomal recessive ataxias (Pt. II-1), *SYNE1* sequencing (Pt. I-2) and mutation carrier testing (Pt. I-1). The nomenclature used for reporting mutations is based on the reference sequence NM_182961.3.

Regular neurological evaluations were performed every 6–12 months on a routine basis. The severity of cerebellar syndrome was rated according to the SARA scale [13].

All procedures were performed in accordance with the ethical standards of the national research committee and with the 1964 Helsinki declaration and its later amendments. We retrospectively described findings from examinations conducted on a routine basis. According with the local regulation, no ethic committee approval was required. Written informed consent was obtained for the genetic testing.

2. Results

2.1. Pure cerebellar ataxia phenotype

Three patients belonging to 2 families showed pure cerebellar ataxia with normal neurophysiological findings and without any signs of cognitive impairment or autonomic dysfunction (I-1, I-2 and II-1 in Table 1). The cerebral MRI showed diffuse cerebellar atrophy with sparing of cerebellar peduncles and brainstem. Disease onset was at the age of 27 (range: 26–27) with gait instability. During follow-up (average 9 years, range: 4–13) only slight, if any, progression of the cerebellar syndrome, was detected. At the last visit the average SARA score was 12 out of 40 points (range: 9–14). In affected individuals from both pedigrees novel homozygous *SYNE1* mutations causing a premature stop codon were detected (see Table 1). After patient II-2 was diagnosed with *SYNE1* ataxia, a brother of her referred to our department because of mild gait ataxia (difficulties in tandem gait) and mild dysarthria noticed since about 1,5 years. His SARA score was 3 out of 40 points. He did not undergo genetic testing and was not referred for follow-up visits.

2.2. Spastic-ataxia phenotype

Two siblings, belonging to family III (see Table 1), displayed a more complex phenotype. Instability of gait was the first symptom recalled, beginning in his twenties in the male sibling (III-1) and as early as at the age of 13 in his sister (III-2). Both had a marked truncal obesity (III-1 BMI = 30), while a third unaffected brother was slim and had normal BMI. The family history was unremarkable.

Patient III-1 was referred for the first time at the age of 31. He presented with spasticity and hyperreflexia, more pronounced in the lower extremities with positive pyramidal signs. Muscle strength was normal, but atrophy and fasciculation of the tongue were evident. Further, dysdiadochokinesia and mild limb dysmetria were present. Dysarthria and marked speech dyspnea were apparent. His SARA score was 11 out of 40 points. He had a normal early development.

His sister was referred at the age of 24. She showed mild spasticity and brisk reflexes in the lower extremities, marked atrophy of hand muscles, mild to moderate paresis both in upper and lower limbs and fasciculations of the tongue. The only evident cerebellar sign was broken up smooth pursuits. She had no dysmetria of upper limbs and coordination of lower extremities could not be examined because of

Table 1
Clinical features of patients with SYNE1 mutations; for comparison see Refs. [11,12] Nomenclature based on SYNE1 Ensembl transcript ENST00000367255.9 which corresponds to NCBI Reference Sequence NM_182961.3 and on SYNE1 Ensembl transcript ENST00000423061.5/NCBI Reference Sequence: NM_033071.3 in in square brackets (where differences between transcripts occur). N.a.: not available/applicable; UE: upper extremities, LE: lower extremities; ** She had oculomotor dysfunction. Limb and gait ataxia could not be examined because of muscle weakness.

Family	Pt. ID	Phenotype category	Genotype	Gender	Age at onset	Age at last visit	Last SARA score	Cerebellar Ataxia	Upper motor neuron dysfunction	Lower motor neuron dysfunction	Cerebellar atrophy (MRI)	Peripheral neuropathy	EMG changes (muscle)	MEPS	Non-motor features
I	I-1	Pure cerebellar	c.5623C > T p.(Gln1875*) homozygous	female	26	39	13	+	-	-	+	n.a.	n.a.	-	-
I	I-2	Pure cerebellar	c.5623C > T p.(Gln1875*) homozygous	male	26	43	14	+	-	-	+	-	-	-	-
II	II-1	Pure cerebellar	c.6721G > T p.(Glu2241*) homozygous	female	27	41	9	+	-	-	+	-	-	-	-
III	III-1	Spastic ataxia	c.20263C > T p.(Arg6755*) homozygous	male	29	36	16	+	Extensor plantar responses, spasticity, hyperreflexia UE and LE	atrophy and fasciculations of the tongue	+	-	Chronic neurogenic	Abnormal LE	Obesity, restrictive lung function, urge incontinence, syncope, sudden death
III	III-2	Spastic ataxia	c.20263C > T p.(Arg6755*) homozygous + heterozygous exon 7 deletion SMN1	female	13	29	n.a.**	+**	Extensor plantar responses, spasticity, hyperreflexia LE	paresis and atrophy UE and LE, tongue fasciculations	+	Motor axonal	Chronic neurogenic	Abnormal LE	Obesity

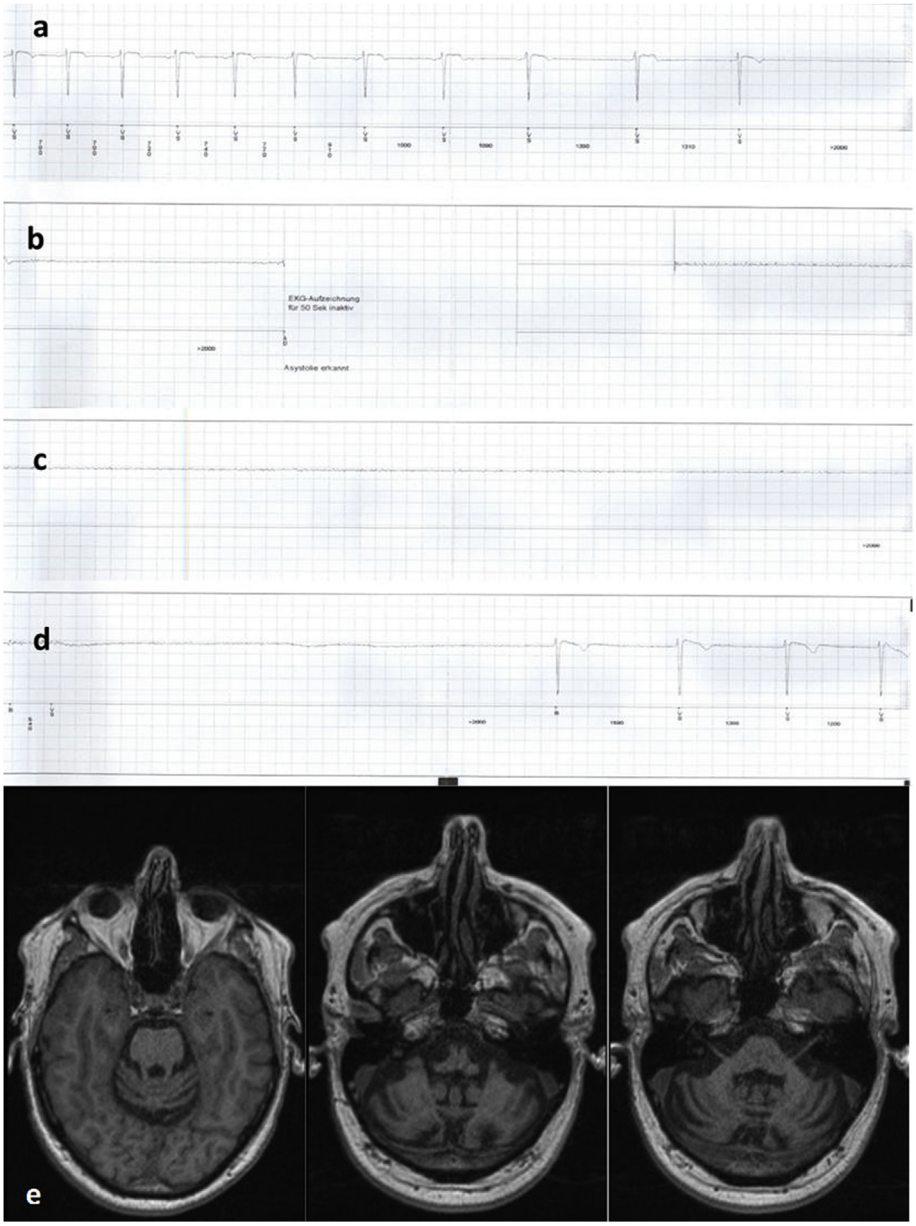

Fig. 1. Clinical findings in patient III-1. (a–d) Loop recorder registration showing 50 s asystole, (e) T1-weighted axial MRI scans showing marked cerebellar atrophy, more pronounced in the vermis, and thin cerebellar peduncles.

muscle weakness. She had a normal early development. At the age of 16, she underwent a muscular biopsy because of suspected spinal muscular atrophy (SMA). Chronic neurogenic changes were described in the *vastus lateralis* muscle. Genetic testing revealed a carrier status for SMA (heterozygous deletion of exon 7).

Both siblings underwent an extensive work-up. Cerebral MRI showed marked cerebellar atrophy, more pronounced in the vermis, with an enlarged fourth ventricle and opened connection to extracerebral subarachnoidal spaces (Fig. 1). No additional cerebral atrophy or white matter lesions were observed. In patient III-1, laboratory evaluations showed recurrent mild to moderate elevation of creatine-kinase (CK) (range 197–467 U/l, upper limit: 190 U/l), with only slight elevation of myocardial specific CK (range 7–19 U/l, normal level < 6). In both siblings, pathologic motor and sensory evoked potentials were found. Neuropsychological testing in patient III-1 revealed marked impairment of verbal and figural memory, attention, executive function, as well as mild impairment of visuo-constructive abilities. *SYNE1* sequencing revealed a novel homozygous truncating mutation (c.20263C > T, rs780451185; p.(Arg6755*)) in both siblings. At their last visit 5 years after first referral, the siblings showed progression of ataxia (SARA score III-1 = 16; worsening of paresis/wheel-chair bound in III-2).

During follow-up, patient III-1 was examined several times because of respiratory and autonomic dysfunction. Pulmonary function testing yielded a restrictive respiratory pattern. He suffered from urge incontinence, and an increased residual urine volume after voiding was documented. Moreover, recurrent syncopal episodes were reported. Syncope occurred in different situations: during physiotherapy or, repeatedly, during blood withdrawal. The patient underwent a tilt-test evaluation during which syncope occurred and an asystole of 77 s was recorded. A vasovagal syncope of cardio-inhibitory type was diagnosed and resulted in an implantation of a cardiac loop recorder which registered another vasovagal asystole of 50 s (Fig. 1). No atrioventricular blocks or tachyarrhythmias were recorded. A cardiac-MRI showed a reduced ejection fraction (40%), hypocontractility and a non-compaction-cardiomyopathy appearance. NTproBNP and high-sensitivity

Troponin-T were within normal ranges (NTproBNP < 50 ng/l; Troponin-T 6.8 ng/l). A VVIR pacemaker, a subtype with no additional defibrillation capacity [14], was implanted and the patient underwent regular check-ups of his device. The patient died of sudden death at the age of 37 years. Autopsy was declined by the parents.

3. Discussion

In the present paper, we describe novel genetic and clinical features of a new independent *SYNE1*-ataxia cohort.

To the best of our knowledge, this is the first report of myocardial involvement in a patient with *SYNE1*-ataxia. Patient III-1 had early signs of structural heart disease, as shown by cardiac MRI. However, the repeated syncopal events clearly presented as typical vasovagal cardioinhibitory syncopes, and neither AV nodal conduction disease nor ventricular tachyarrhythmias were detected by an implanted loop recorder. Therefore, a conventional pacemaker without defibrillation capacity (ICD) was implanted after documentation of a long asystolic event. Only mild systolic left ventricular dysfunction was diagnosed, well above the established ejection fraction cut-off of 35% or below usually indicating primary ICD prophylaxis [14]. In retrospect, the tragic event of early sudden cardiac death and some features in cardiac MRI, like signs of left ventricular non-compaction, may indicate a rather malign form of cardiomyopathy.

The unremarkable family history and the absence of further cardiovascular risk factors led us to speculate a role of the underlying genetic disorder in the pathogenesis of cardiomyopathy, although we cannot exclude pathogenic variants in different genes associated with sudden cardiac death.

The *SYNE1* mutation detected in our family with a complicated phenotype localizes close to the C-terminus (see Fig. 2), while those associated with pure cerebellar ataxia are located nearer to the N-terminus. In the largest *SYNE1*–ataxia cohort reported to date [12], mutations associated with additional motor neuron signs spanned over the entire gene. Nonetheless, patients with a particularly severe phenotype (including CK elevation, respiratory distress and premature death) bore C-terminal mutations (see Fig. 2) [8,12], collectively supporting a genotype-phenotype correlation.

At least 30 nesprin-1 variants can be generated via alternative initiation/splicing. Recently, a Nesprin-1 isoform devoid of KASH domain has been identified (KLNes1g), which is expressed specifically in central nervous system [15]. This isoform is particularly abundant in the cerebellum, where it colocalizes with synaptic vesicles in mossy fibers. All *SYNE1*-ataxia related mutations are expected to lead to truncation of KLNes1g and thus the dysfunction of this isoform is predicted to underlie the cerebellar phenotype. Though, the pathophysiological basis of additional non-cerebellar features remains unclear. Interestingly, heterozygote missense *SYNE1* mutations localizing at C-terminus have recently been associated with muscular disorders such as Emery-Dreifuss muscular dystrophy (EDMD) [16] and dilated cardiomyopathy [17]. EDMD and dilated cardiomyopathy have a heterogeneous genetic background, and in both diseases mutations in proteins related to the nuclear membrane, such as emerin and laminin A/C, are involved [18,19]. Emerin and laminin A/C mutations result in perturbation of the proteic complex that connects nucleoskeleton and cytoskeleton (LINC) [16,17]. *SYNE1* missense mutations associated with EDMD and dilated cardiomyopathy affect Nesprin-1 domains involved in binding to the LINC may result in similar cytoarchitectural alterations [16,17]. In turn, LINC perturbations lead to impairment in myoblast differentiation and fusion, accounting for the final myopathic phenotype [16,17,20]. In complicated *SYNE1*-ataxia, C-terminal truncating mutations may result in a mixed phenotype by affecting expression of the short isoforms which are prevalently expressed in heart and skeletal muscle [1,15] or by acting synergic with polymorphisms in other key proteins.

The typical MRI finding in *SYNE1*-ataxia is an isolated diffuse cerebellar atrophy as seen also in our patients with pure cerebellar phenotype [3]. Hypometabolism of the pons at FDG-PET or multiple sclerosis-like white matter lesions have been reported in single cases [12,21]. In our report, the siblings with a complicated phenotype

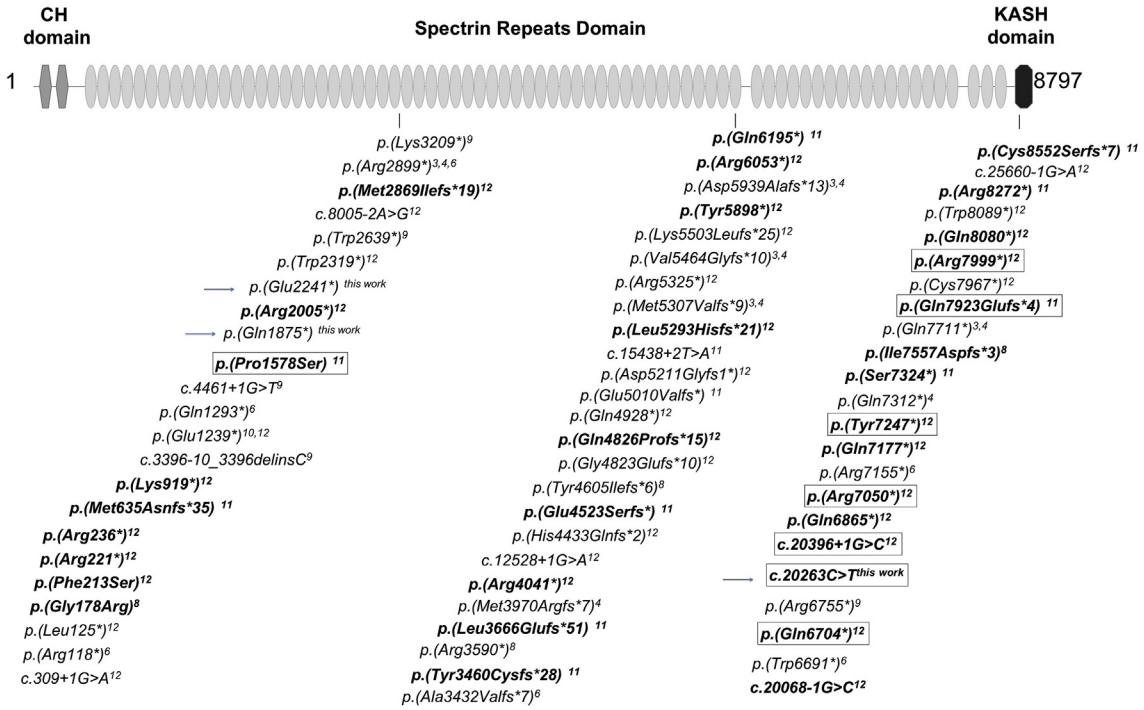

Fig. 2. The longest nesprin isoform is shown schematically. The mutations associated with cerebellar ataxia up to date are reported with the respective literature reference. Mutations associated with additional motor neuron signs are reported in bold. Among the latter, the mutations associated with a severe phenotype (see text) are framed. Arrows indicate the novel genotypic variants identified in this study. N.b.: the mutation p.(Pro1578Ser) is associated with a C-terminal mutation p.(Gln7923Glufs*4) in a patient with a severe phenotype. Nomenclature based on SYNE1 Ensembl transcript ENST00000367255.9 (see also Table 1 caption).

displayed an atypical MRI pattern, with severe atrophy of the *vermis cerebelli* and additional involvement of cerebellar peduncles.

Another peculiarity in our cohort is represented by the striking phenotypical variability in the sibship with complicated phenotype. First of all, a marked difference concerning age at onset was observed. Moreover, spasticity and hyperreflexia were the main findings in the brother, whereas the sister showed diffuse amyotrophy and paresis, while marked cerebellar atrophy was present in both. Since a SMA carrier status was detected in the female sibling (patient III-2) during diagnostic work-up, a modifying effect of this additional genetic factor on the phenotype presentation in patient III-2, although speculative, could be hypothesized. Further, planed evaluation in our siblings in this respect was hampered by the unexpected, sudden death of the brother. The patients with pure cerebellar ataxia had a very homogeneous clinical phenotype as previously described [3].

4. Conclusion

In conclusion, our report confirms previous descriptions of *SYNE1*-ataxia and adds novel findings concerning genetics and clinical phenotype. The present findings suggest that screening for cardiomyopathy should be performed in patients with an overt motor neuron involvement.

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Conflicts of interest

Nothing to declare.

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