SYNE1-related autosomal recessive cerebellar ataxia, congenital cerebellar hypoplasia, and cognitive impairment

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Abstract

The spectrin repeat-containing nuclear envelope protein 1 (*SYNE1*) gene encodes a family of spectrin structural proteins that are associated with anchoring the plasma membrane to the actin cytoskeleton. *SYNE1*-related disease is most commonly reported in autosomal recessive spinocerebellar ataxia 8, which demonstrates variable age of onset with a median of 30 years of age. However pathogenic mutations in *SYNE1* are also causative of arthrogryposis multiplex congenital, a severe congenital neuromuscular condition. Here in we report monozygous twins with childhood onset ataxia, cerebellar hypoplasia, dysarthria, and cognitive impairment sharing two novel heterozygous mutations in the *SYNE1* gene. Our family may expand the clinical phenotype associated with *SYNE1*-related disease and offers possible genotype-phenotype correlations of a rare continuum of clinical disease phenotypes from neonatal to adult onset.

Introduction

The spectrin repeat-containing nuclear envelope protein 1 (*SYNE1*) gene (OMIM 608441) is located on chromosome 6q25 and contains 146 exons.[1] *SYNE1* mutations are most commonly associated with an adult onset cerebellar ataxia, autosomal recessive spinocerebellar ataxia 8, autosomal recessive cerebellar ataxia type 1 (ARCA1), or Ataxia of Beauce (OMIM 610743).[2-4] *SYNE1*-related autosomal recessive ataxia typically presents with ataxia, dysarthria, and executive function difficulties such as visuospatial awareness and working memory. The onset is usually in the middle-aged years with slow progression of the disease to generate moderate levels of neurodisability, but no impact on life expectance.[5]

SYNE1-related autosomal recessive ataxia is most commonly reported in Quebec, Canada with a sparse number in other countries such as Japan or Saudi Arabia.[2,3,5-7] *SYNE1* mutations are a common cause of autosomal recessive ataxia of adult onset.[8] Pathogenic mutations in *SYNE1* have recently been associated with an arthrogryposis multiplex congenital (AMC).[4,9] *SYNE1*-related disease represents a continuum of clinical disease phenotypes from neonatal to adult onset. Here in we report monozygous twins with childhood onset ataxia and cerebellar hypoplasia associated with rare heterozygous mutations in the *SYNE1* gene. Our family expands the clinical phenotype associated with *SYNE1*-related disease and offers possible genotype-phenotype correlations.

Case Report

This monochorionic monoamniotic twin pregnancy was the product of *in vitro* fertilization to an otherwise healthy Caucasian couple. The pregnancy was uncomplicated with the twin girls being delivered *via* elective lower segment caesarean section at 38 weeks of gestation. Both girls were born in good condition with Apgar scores of 9 at 1 minute and 9 at 5 minutes. Twin 1 and twin 2 had weights of 2.8kg and 2.9kg respectively, and head circumferences of 33cm and 34 cm respectively. They first presented for medical evaluation at 5 months of age with parental concerns of hypotonia and developmental delay. All facets of developmental modalities have been delayed, especially gross motor, speech and language domains. There has been no developmental regression. They crawled at 2.5 year of age, and walked at 3.5 years of age. Currently at 13 years of age they can ambulate independently and safely. They have a narrow-based gait but are unable to tandem walk. They have normal power, but reduced tone. Deep tendon reflexes were reduced and Romberg's test is positive. Visual acuity is 6/6, they have a mild alternating strabismus, and nystagmus on lateral gaze. Expressive language acquisition has been delayed. At 13 years of age they can speak in short truncated sentences, with articulation and phonological difficulties. Formal psychometric assessments were performed at 12 years of using Stanford-Binet intelligence scales 5th edition. These scales found that fluid reasoning, quantitative reasoning, visual spatial processing, and working memory all indicated a result below the 1st percentile. They are not dysmorphic.

An MRI brain and spine completed at 8 months and 16 months were reported normal. Subsequent MRIs at age 9 years showed evidence of moderate cerebellar hypoplasia of both hemispheres and the cerebellar vermis. Extensive investigations failed to identify an aetiology including plasma and urine amino acids, urine metabolic screens, thyroid function tests, liver function and creatine kinase, full blood count, very long chain fatty acids, transferrin isoforms, vitamin E levels, alpha-fetoprotein, and CSF neurotransmitters/lactate/glucose/protein. A SNP array was normal as was an ataxia gene panel. Nerve conduction studies completed at 10 years were essentially normal (Table 1).

Genome wide exome sequencing was performed in the laboratories of MyGenomics (http://www.mygenomics.

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com/) in the USA. After enrichment of all the coding and flanking intronic regions, sequencing analysis was performed using an Illumina HiSeq platform. The quality criteria required at least 10 reads per base, however, 97.7% of targeted regions achieved x100 coverage and 99.7% achieved x10 coverage. Only sequence variations with an allele frequency <1% were considered pathogenic. We identified two rare heterozygous sequence variations: variant 1 NM_033071 c.17878G>A p.(Glu5960Lys) and variant 2 NM_033071 c.10805A>G p.(Asn3602Ser) in the *SYNE1* gene. Both variants were confirmed *via* sanger sequencing in the twins and the parents confirmed to be heterozygous carriers, the father for variant 1 and the mother for variant 2. Both sequence variants are listed on dbSNP ID rs142229551 with an allele freq 5.77e-05 (ExAC) and ID rs148212715 with an allele freq 0.0001483 (ExAC). Both variants were identified in the heterozygous state and classified as variants of unknown significance on one occasion by two different laboratories using targeted sequencing panels.

The NM_033071 c.17878G>A p.(Glu5960Lys) variant is predicted to be a missense mutation. The BLOSUM62 substitution matrix reports a score of 1 for this alteration. The amino acid substitution is predicted to be tolerated (SIFT score: 0.06). This variant overlaps with evolutionary constrained element (detected using SiPhy-ω and SiPhy-π statistics). The conservation across 28 species is described with PhyloP (score: 0.75). GERP identifies constrained elements in multiple alignments by quantifying substitution deficits (score: 3.85). The amino acid change is within the 53rd Spectrin repeat region.

The NM_033071 c.10805A>G p.(Asn3602Ser) variant is predicted to be a missense mutation. The BLOSUM62 substitution matrix reports a score of 1 for this alteration. The amino acid substitution is predicted to be damaging (SIFT score: -1.00). The variant overlaps with evolutionary constrained element (detected using SiPhy-ω and SiPhy-π statistics). The conservation across 28 species is described with PhyloP (score: 0.08). GERP identifies constrained elements in multiple alignments by quantifying substitution deficits (score: -1.49). The amino acid change is within the 32nd Spectrin repeat region.

Discussion

The *SYNE1* gene is large containing 146 exons and encodes a family of spectrin structural proteins that are associated with anchoring the plasma membrane to the actin cytoskeleton playing key roles in cytoskeletal, nuclear, and vesicle anchoring.[1,10] The protein product is expressed in multiple tissues throughout the body, with an abundance in the cerebellum.[1] The *SYNE1* protein products, including the Nesprin-1 and Nesprin-2 isoforms, comprise of 2 N-terminal actin-binding regions with tandem paired calponin homology domains, transmembrane domain and spectrin repeats.[2,4] At the C-terminus of the isoforms, there is a Klarsicht homology domain. Nesprin-1 and 2 also contain central rod domains contain spectrin repeats which function to bind dynein and kinesin as well as dimer formation.[4]

Nonsense mutations in *SYNE1* exons 56, 71, 93, 118, 126 or in introns 81 and 84 have been identified in ARCA1.[4] These mutations are in the N-terminal regions outside the emerin and lamin binding domains and likely result in severe loss-of-function of the larger isoforms which may also affect brain specific isoforms. Truncating recessive *SYNE1* mutations have been described as a cause of an arthrogryposis multiplex congenital syndrome,[5,10] where the mutation truncates nesprin-1 isoforms for the C-terminal KASH (Klarsicht-ANC-Syne homology) domain. Research has shown that mice lacking the KASH domain of nesprin-1 display a myopathic phenotype.[10] From this research, it could be inferred that mutations of nesprin-1, which interacts with lamin A/C, may lead to at least two distinct human disease phenotypes, myopathic or neurological.[4] Both variants identified in our patients occur within the spectrin repeat region of the gene. The spectrin repeat region is thought to be important in maintaining the elongated shape of the protein dimer and hence, the function of the protein product.

Conclusions

SYNE1 mutations are most commonly associated with an adult onset ARCA1, however, there is emerging clinical phenotypic diversity of *SYNE1*-related disease in the non-French Canadian population.[8] This is especially evident with the research

Table 1. Summary of early onset SYNE1-related cases.

	Our patient	[2]	[2]	[2]	[2]	[4]	[4]	[1]	[1]	[3]	[6]	[6]
Consanguineous	-	-	-	+	-	+	+	-	-	+	-	-
Hypotonia	+	-	-	-	-	+	+	-	-	+	-	-
Developmental delay	+	-	-	-	-	-	-	-	-	+	-	-
Ocular issues	+	+	+	+	-	-	-	+	+	+	+	+
Delayed expressive language acquisition	+	-	-	-	-	-	-	-	-	-	-	-
Cerebellar hypoplasia	+	+	+	+	+	MRI absent	MRI absent	MRI absent	+	MRI absent	+	+
Gait abnormalities	+	+	+	+	+	+	+	+	+	+	+	+
Reduced reflexes	+	-	-	-	+	-	-	-	+	+	-	-
Intellectual impairment	+	-	+	+	+	-	-	+	-	+	-	-
Clubfoot	-	-	-	-	-	+	+	-	-	+	-	-
Variant	Variant 1: NM_033071 c.17878G>A p.(Glu5960Lys) Variant 2: NM_033071 c.10805A>G p.(Asn3602Ser)	Compound heteroxygous Exon 18 (c.1894G>T: p.E617X) and exon 99 (c.18431G>A: p.W6144X)	Exon 108 (c.19897C>T p.Q6633X)	Truncating homozygous exon 77 c.13429C>T : p.Q4477X	Not described	Not described	c.9153A>AT p.R2906X	c.26236C>T	Exon 78: c.14091G>T (p.Met4697Ile) Exon 92 c17483C>G (p.Thr5828Arg)			

describing non-cerebellar manifestations to be common including complex neuromuscular syndromes.[8] This disease then represents a clinical spectrum of symptoms and severity, and to date our cases are the only ones reported to have predominantly a congenital cerebellar hypoplasia phenotype. Our cases, with their novel missense mutations, provide a phenotypic link between the book ends of the *SYNE1*-related disease spectrum or AMC and ARCA1.

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