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ORIGINAL ARTICLE

A novel homozygous mutation in spectrin beta chain, nonerythrocytic 4, with syndromic neurodevelopmental phenotype in a consanguineous family of Saudi origin

Raja Hussain Ali[1*], Muhammad Umair[1]

ABSTRACT

Background: Genetic neurological disorders are both clinically and genetically heterogeneous. Among them, neurodevelopmental disorder with hypotonia, neuropathy, and deafness (NEDHND, OMIM #617519) is a rare autosomal recessive genetic syndromic condition. This study is aimed to characterize the underlying genetic cause of mutisystemic dysfunction in a single consanguineous family of Saudi origin.

Methods: This study investigated the causal genetic changes in the affected family member with neurological issue and deafness issues along with muscular weakness using unbiased whole genome sequencing.

Results: The genetic investigation uncovered a novel missense change (c.5501G>A; p.Arg1834Gln) in the exon 26 Of *SPTBN4* gene located on 19q13.2, which segregated in accordance with the autosomal recessive inheritance model.

Conclusion: This study establishes a genotype-phenotype correlation for the neurodevelopmental disorder with hypotonia, neuropathy, and deafness (NEDHND, OMIM #617519) and reinforces the concept that variants of uncertain significance, including the one found in this report, hold yet to be fully uncovered role in influencing the gene specific phenotypes for a particular genetic condition.

Keywords: Novel mutation, SPTBN4, NEDHND, syndromic neurological disorder.

Background

Cellular homeostasis not only requires orchestrated physiological and molecular activities but also a flawless structural framework in order to enable myriad of cellular processes. Spectrin is one such structural protein that reinforces the cytoskeleton and clusters Na+/K+ channels at the axon initial segment (AIS) and at the nodes of Ranvier via interaction with ankyrin-G, in the neurons (1,2). The spectrin proteins in vertebrates are heterotetramers with two α- and two β-subunits. There are two members (I and II) in α-spectrin subgroup and five members (I–V) in the β-spectrin subgroup (3,4).

SPTBN4 (spectrin beta chain, nonerythrocytic 4) is one of the βIV-spectrin that is enriched in myelinated neurons of the central nervous system (5). Pathogenic mutations in *SPTBN4* result in autosomal recessive neurodevelopmental disorder with hypotonia, neuropathy, and deafness (NEDHND, OMIM #617519) (6–8), which is a rare neurodevelopmental disorder with syndromic presentation. Here, we report the clinical and genetic characterization of a consanguineous kindred showing classical neurological features and associated muscular and hearing impairment consistent with NEDHND. The exome analysis revealed a novel missense mutation (c.5501G>A; p.Arg1834Gln), the gene SPTBN4. The Sanger sequencing showed perfect segregation of

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identified variant among the family members that was in accordance with autosomal recessive transmission.

Our report further strengthens the findings that the NEDHND is genetically heterogeneous disorder with some degree of variation in the clinical presentation. Moreover, this identification of novel mutation in *SPTBN4* also suggest yet to be explored role played by variants of unknown significance in mediating a disease phenotype.

Materials and Methods

Ethical approval

For the current study, a consanguineous family was enrolled for identifying the genetic changes responsible for syndromic neurological finding in a single patient. In accordance with the Helsinki Declaration guidelines, a written informed consent in native language (Arabic) of the family was obtained from the parents for collecting blood samples, radiography, and other necessary lab tests along with the dissemination of the results obtained in a research journal. The research was started upon approval of institutional review board (IRB) from the King Abdullah International Medical Research Center (KAIMRC).

Genomic DNA extraction and quantification

The pedigree was drawn by taking thorough family history from the parents. The affected boy was born to a consanguineous marriage, and pedigree shows classical autosomal recessive inheritance pattern. The DNA was extracted and quantified from the peripheral blood samples from the available family members using standard protocols as reported in earlier studies (9).

Whole Exome sequencing

In order to identify the underlying genetic cause of NEDHND in the enrolled family, an unbiased genetic approach called whole exome sequencing (WES) was performed in both parents and the proband as described earlier (10). Briefly, for WES, the extracted genomic DNA was enzymatically digested followed by library preparation by adding Illumina-compatible adapters and libraries through PCR. The prepared libraries were paired and then sequenced on an Illumina platform, producing 30× coverage depth on an average. The aligned reads mapped to GRCh37/hg19 genome assembly, followed by variant calling and annotations by standard methods using an in-house bioinformatics pipeline. In order to identify the causal mutation in the proband, the threshold criteria were set where the variants with minor allele frequency (MAF) of less than 1 % in the gnomAD database, as well as disease-causing variants reported in HGMD®, ClinVar, or CentoMD®, were considered significant. While coding exons and flanking ± 30 intronic bases were the primary focus, the entire gene region was searched for candidate variants with a plausible association with the phenotype. The DRAGEN pipeline from Illumina was used to call the structural variants (SVs). Based on the inheritance mode in the pedigree, the homozygous and compound heterozygous variants were filtered. Furthermore, the clinical information were used to assess the pathogenicity and causality of the identified variants. They were classified into five groups: pathogenic, likely pathogenic, variant of uncertain significance (VUS), likely benign, and benign. All the variants related to the patient's phenotype were investigated. Orthogonal methods confirmed the variants of low-quality and/or unclear zygosity. The identified variant was screened in gnomAD, 1,000 genomes, and in-house (2,000) genomes/exomes from the Saudi population.

Sanger sequencing

After WGS filtration, the shortlisted variants were verified for segregation using Sanger sequenced in all the available family members using primers designed from the exon flanking the mutation.

Results

Clinical findings

The proband in the consanguineous family (Figure 1) enrolled for this study was a 9-year-old boy, who was born to a full-term pregnancy. The boy presented with muscular hypotonia during first 3 months and delayed neurodevelopmental milestones, including inability to crawl, delayed speech, and motor responses. The loss of hearing was also observed by the mother of proband based on his inability to respond to his name and to any loud sound, which would otherwise trigger an immediate response in kids with normal hearing. However, the audiometric test to assess the extent of deafness and CT scan of brain was not performed due to patient's inability to comply for these diagnostic tests. The imaging

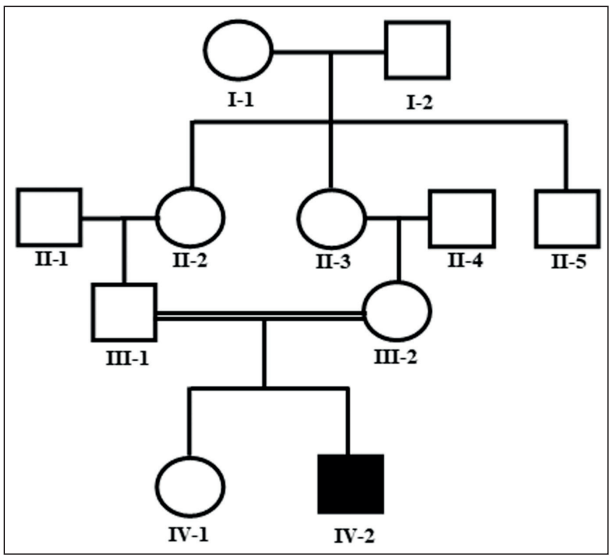

Figure 1. *Pedigree of the family with NEDHND (OMIM: 617519). The proband in fourth generation is shown in dark.*

studies using ultrasound and CT-scan suggested bilateral peribranchial wall thickening, consistent with small airway disease. Another finding in the thoracic region was the presence of left retrocardiac air space opacity silhouetting left hemidiaphragm, which possibly suggest early pneumonic infiltration/atelectatic changes. There were no signs of pleural effusion in lungs. The imaging in thoracic region also suggested a generalized reduction in bone density that fits in with generalized osteoporosis (Figure 2). The imaging for abdominal region was unremarkable except the finding of grade 1 and grade 2 hydronephrosis in right and left kidneys, respectively.

WES and Sanger sequencing

To establish the genetic characterization of the affected individuals, WES sequencing was performed. The analysis of sequencing data was performed primarily based on the autosomal recessive inheritance shown in pedigree, and the homozygous variants were filtered through different criteria, including MAF using gnomAD, splice site (±30 bp), and the variants that correlate with the syndromic neurodevelopmental phenotype reported here. Filtering of variants based on the above criteria revealed few mutations in the homozygous state; among them, only one variant perfectly lines up with the three prong inclusion criteria (homozygous, MAF < 0.01, and the gene with the mutation show similar/overlapping phenotypes in previous reports).

This three prong filtering revealed a homozygous missense variant [c.5501G>A; *p*. (Arg1834Gln)] (rs766117476) in exon 26 of SPTBN4 (NM_020971.3; OMIM 617519). This minor allele frequency of this missense variant is 0.00002055 in the gnomAD/Exomes; however, the variant was not reported in a homozygous state in in-house (2,000) genomes/exomes from the Saudi population or in gnomAD. The variant is classified as a variant of unknown significance (UVS) by CLinVar, Franklin, and ACMG.

The mutation segregation was confirmed through Sanger sequencing. The father and mother were carrying one mutant allele and one wild-type allele (show heterozygosity for this mutation), and the control sibling has two normal alleles (homozygous for the wild-type allele), while the proband has two mutant allele (homozygous for the mutation). Thus, the Sanger sequencing showed that the mutation segregation perfectly followed the autosomal recessive mode of inheritance. No copy number variations that correlated to the observed phenotype were found during the analysis.

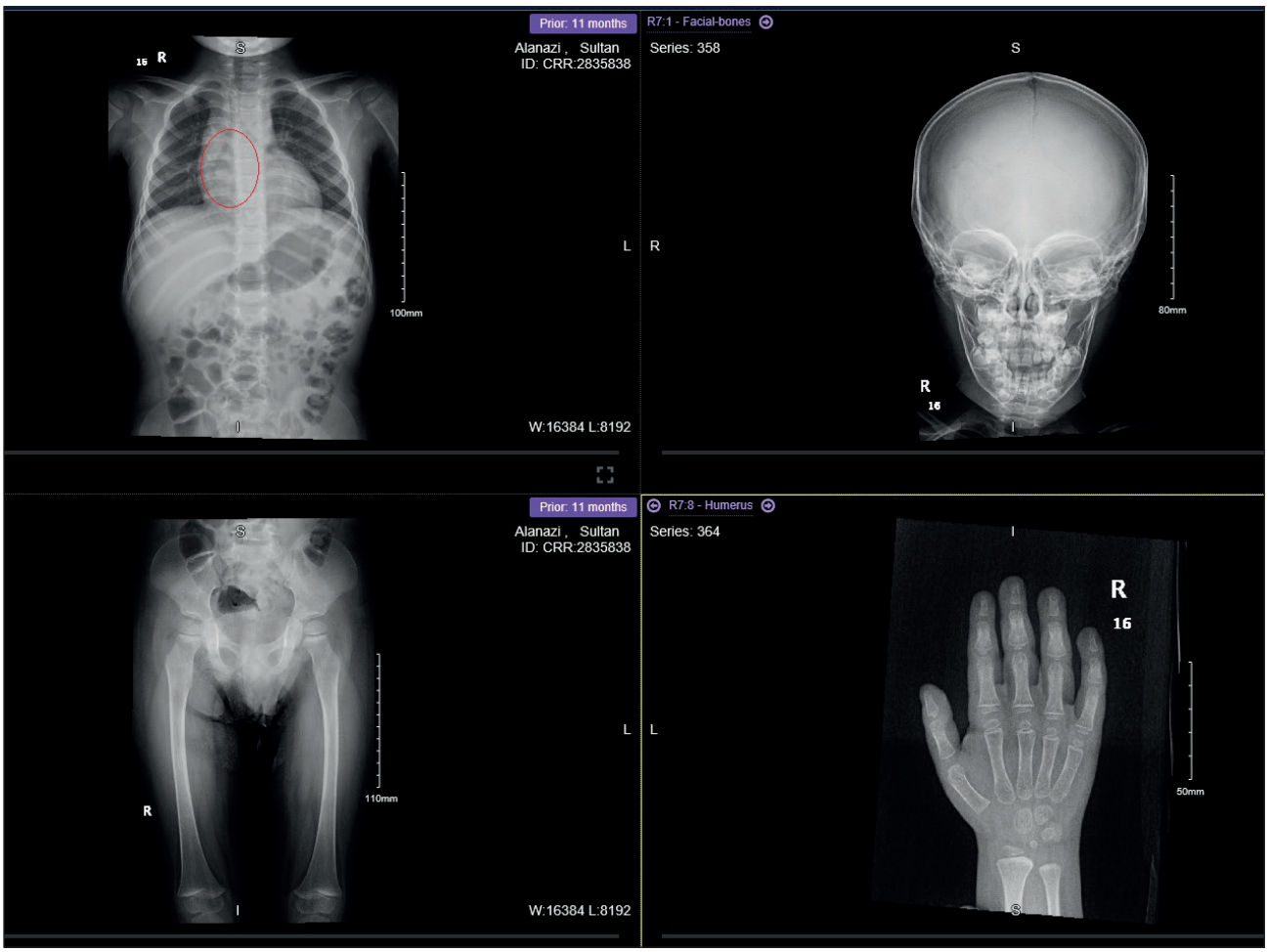

Figure 2. *X-rays showing pulmonary and skeletal findings.*

Discussion

The spectrins are ubiquitously expressed in the nervous system of humans and establish neuronal homeostasis by various means, including positioning and stabilization of the domains of ion channels, coordinating cellular signaling and furnishing mechanical strength, and facilitating organelle and vesicle transport (11). The spectrins are heterotetrameric in their organization, constituted by two α- and two β-subunits. They are further classified into α-spectrins (two members, I and II) and β-spectrins (five members, I-V). Disruption in the normal functioning of these multifaceted proteins manifests as a range of neurodevelopmental phenotypes, which are collectively termed as spectrinopathies (8). *SPTBN4* (spectrin beta chain, nonerythrocytic 4) is the fourth member of β-spectrin subgroup. This nonerythrocytic member of the β-spectrin family of proteins scaffolds the cytoskeleton framework of the neurons (12). Pathogenic mutations in SPTBN4 manifest as a rare genetic condition with syndromic features, including neurodevelopmental disorder with hypotonia, neuropathy, and deafness (NEDHND, OMIM #617519). This syndrome is transmitted in autosomal recessive fashion.

Here, we report a novel missense mutation (c.5501G>A; p.Arg1834Gln) in the gene *SPTBN4*, in a consanguineous kindred with classical neurological features and associated muscular and hearing impairment. The architectural changes in the brain of proband were not available due to difficulties in performing brain MRI; however, the lack of neurodevelopmental milestones (inability to speak and motor delays) strongly suggests abnormal brain functioning. Likewise, the precise degree of hearing loss was not established, but the lack of reflex of proband to loud voices reflects severe defects in hearing. The radiography identified bilateral peribronchial wall thickening, which is consistent with small airway disease, while the presence of left retrocardiac air space opacity suggests early pneumonic infiltration/atelectatic changes. In addition to the above findings, osteoporosis was also documented, which is a rare phenotype in NEDHND.

To date, 30 mutations are identified in SPTBN4 for single gene disorders causing neurodevelopmental phenotypes, including 13 missense, 5 nonsense, 3 splice site, 7 deletions, 1 duplication, and 1 regulatory mutations (Table 1). However, recent studies have showed that de novo mutations identified in SPTBN4 through integrated genome analysis are associated with autism, which is a common neurological condition (13,14). Interestingly, all of the missense variations identified in these two association studies are predicted as UVS by various online tools that predict pathology based on nucleotide change. This plausibly suggests that SPTBN4 plays a much broader role in neuronal homeostasis compared to original significance in neurodevelopment uncovered through NEDHND as a single gene disorder.

Wang et al. (8) reported five families with unique mutations in SPTBN4, surprisingly the proband with UVS in showed strikingly similar phenotypes compared to patients with a missense or a frameshift mutations that resulted in protein truncation. Through the functional studies, the authors showed that in the localization experiment of human SPTBN4 in cultured rat hippocampal neurons, the truncated STPBN4 was absent at AISs, which is co-localized with ankyrinG (AnkG) in the case of full length wild-type protein, surprisingly both UVSs (p.Arg504Gln and p.Arg2435Cys) were targeted to AIS, despite producing classical phenotype of NEDHND. Further investigation of this interesting observation through pull down assay revealed that AnKG interaction with full length SPTBN4 is necessary for localization to AIS. Moreover, the UVS p.Arg504Gln despite being able to bind AnKG and localized to AIS shows the phenotypes of NEDHND because the UVS is present in the spectrin repeat 2 domain, which underlie α and β subunit heterodimer interactions in mature SPTBN4 protein.

Interestingly, the UVS (c.5501G>A; p.Arg1834Gln) identified is located in the exon 26 of SPTNB4 gene, which contributes to part of the 15th SR domain (Figure 3A) that is known to interact with AnKG. Thus, the UVS here is most plausibly translating into disease phenotype through disruption of AnkG interaction resulting in mislocalization of SPTBN4 with AIS. The mutated amino acid arginine shows perfect conservation across multiple species (Figure 3B). This is expected to primarily disrupt neuronal development and scaffolding that manifest as neuronal abnormalities in hearing, vision, and motor delays, while based on one of the previous reports (6) the disrupted organization of Na+/K+ channels in myelinated neurons deregulate the initiation or propagation of the depolarization waves along the myofiber and its T-tubular system, which results in hypotonia phenotype.

Among the various types of genetic mutations, the VUSs are proving much more difficult to predict their functional effect in generating a phenotype. One explanation to that is the very nature of the VUS, which substitute one amino acid with other, compared to other mutation classes (nonsense, splice site, structural variant, insertion, and deletion) that mostly produce a quantifiable change in protein expression and downstream targets. With the help of advances in sequencing platforms and technologies, an unprecedented amount of large-scale genomic data across different populations is available. It is the need of time to develop effective tools/assay to robustly access the role of UVS in disease biology not only for research purposes but also for diagnostic, genetic counseling, and noninvasive prenatal genetic testing avenues (15).

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Table 1. *Known mutations in SPTBN4 causing neurodevelopmental phenotypes.*

Mutations known in SPTBN4 (30 mutations in this table)					
Codon/Nucleotide change	**Mutation**	**Protein change**	**Mutation class**	**Phenotype(s) observed**	**Reference publication**
CGG-CAG	c.5501G>A	p.Arg1834Gln	Missense	Neurodevelopmental disorder with hypotonia, neuropathy, and deafness	This study
AAC-AAA	c.60C>A	p.N20K	Missense	Autism	14
AAA-AAT	c.510A>T	p.K170N	Missense	Autism	14
ATG-TTG	c.793A>T	p.M265L	Missense	Autism	14
CGT-TGT	c.1528C>T	p.R510C	Missense	Autism	14
ACA-ATA	c.5399C>T	p.T1800I	Missense	Autism	14
CGC-CCC	c.737G>C	p.R246P	Missense	Neurodevelopmental disorder with hypotonia, neuropathy, and deafness	6
CTG-CGG	c.3797T>G	p.L1266R	Missense	Neurodevelopmental disorder with hypotonia, neuropathy, and deafness	17
CTG-CCG	c.1217T>C	p.L406P	Missense	Microcephaly, speech delay, intellectual disability, spasticity, and contractures	18
GAG-AAG	c.4831G>A	p.E1611K	Missense	Autism spectrum disorder	19
CGG-TGG	c.5158C>T	p.R1720W	Missense	Developmental disorder	20
CAC-TAC	c.7585C>T	p.H2529Y	Missense	Neurodevelopmental disorder with hypotonia, neuropathy, and deafness	17
CGC-TGC	c.7303C>T	p.R2435C	Missense	Hypotonia, intellectual disability, and motor axonal and auditory neuropathy	8
CAG-TAG	c.1597C>T	p.Q533*	Nonsense	Myopathy, neuropathy, and central deafness	7
TGG-TGA	c.2709G>A	p.W903*	Nonsense	Hypotonia, intellectual disability, and motor axonal and auditory neuropathy	8
GAG-TAG	c.3820G>T	p.E1274*	Nonsense	Hypotonia, intellectual disability, and motor axonal and auditory neuropathy	8

(Continued)

Mutations known in SPTBN4 (30 mutations in this table)					
Codon/Nucleotide change	Mutation	Protein change	Mutation class	Phenotype(s) observed	Reference publication
CAG-TAG	c.3823C>T	p.Q1275*	Nonsense	Autism spectrum disorder	19
CGA-TGA	c.6016C>T	p.R2006*	Nonsense	Profound psychomotor development arrest, hypotonia, cardiomyopathy, and mitochondrial dysfunction	21
T-C	c.1665+2T>C	N/A	Splice site change	Speech delay, intellectual disability, ataxia, seizures, and cerebral atrophy	18
G-A	c.3654+1G>A	N/A	Splice site change	Developmental disorder	15
G-A	c.3949-1G>A	N/A	Splice site change	Axonal neuropathy and hypotonia	22
(G-A) -100 relative to transcription initiation site	c.-420G>A	N/A	Regulatory mutation	Autism spectrum disorder	23
CGGGAG^{415}GCTGcCCTACGGGCT	c.1249delC	p.(Leu417Tyrfs*5)	Small deletion	Neurodevelopmental disorder	6
GCAGGAG^{632}CAGgCAGCGCGGCG	c.1897delG	p.(Ala633Glnfs*110)	Small deletion	Neurodevelopmental disorder	16
TAGAA^{1124}GAGGCggacgcgctgctggcgcgcCACGCTGCGC	c.3375_3393del19	p.(Asp1126Thrfs*39)	Small deletion	Neurodevelopmental disorder with hypotonia, neuropathy, and deafness	6
GCTGGCG^{1131}CGCcACGCTGCGCT	c.3394delC	p.(His1132Thrfs*39)	Small deletion	Intellectual disability	24
GGAGCAG^{1276}GCTcAGGAGGCTGT	c.3829delC	p.(Gln1277Argfs*4)	Small deletion	Hypotonia, intellectual disability, and motor axonal and auditory neuropathy	8
CAGCGAG^{2484}GTGgCTAGTGACTA	c.7453delG	p.(Ala2485Leufs*31)	Small deletion	Hypotonia, intellectual disability, and motor axonal and auditory neuropathy	8
GCGTGCC^{383T}GCcAACCGTCGCC	c.1149dupC	p.(Asn384Glnfs*17)	Duplication	Neurodevelopmental disorder with hypotonia, neuropathy, and deafness	6
Gross deletion	N/A	N/A	Deletion	Neurodevelopmental disorder with hypotonia, neuropathy, and deafness	6
GCCGCTGCCCTGC^{1798}GCTTCTCCCAG	c.1799-1800delGC	p.Arg600Leufs*90	Deletion	Neurodevelopmental disorder with hypotonia and neuropathy.	13

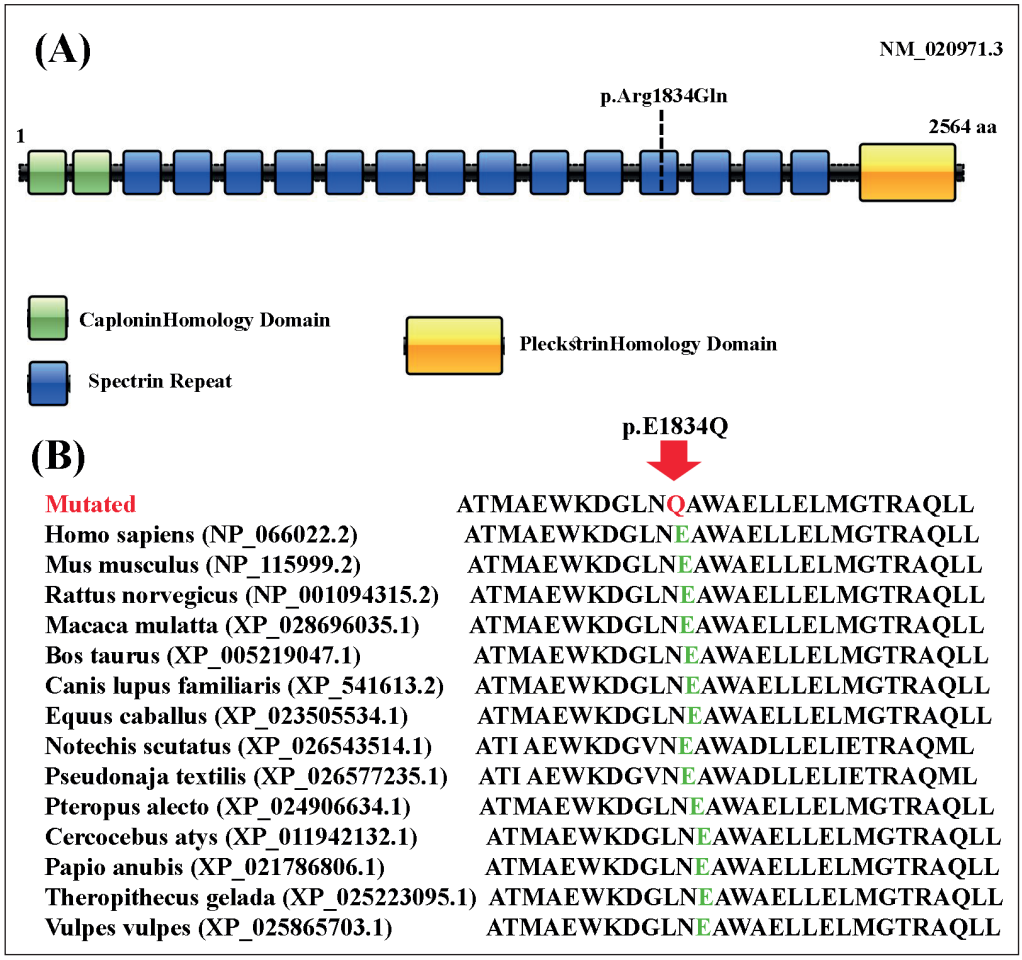

Figure 3. *(A) SPTBN4 protein schematic, showing the different domains in colours. The novel mutation identified is marked with dashed line corresponding to respective spectrin repeat. (B) The conservation of mutated amino acid in mature SPTBN4 is shown across multiple species.*

List of Abbreviations

NEDHND	Neurodevelopmental disorder with hypotonia, neuropathy, and deafness
SPTBN4	Spectrin beta chain, nonerythrocytic 4

Declaration of conflicting interests

The authors declare that they have no conflict of interest regarding the publication of this article.

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Ethics statement

Written informed consent was obtained from the patients.

Authors contributions

Raja H Ali: drafted the manuscript. All the authors reviewed and edited the manuscript and agreed on the final form.

Ethical approval and consent to participate

The study was approved by the research committee [IRB/1470/24] of KAIMRC in Riyadh, Saudi Arabia. The parents of the patient provided written informed consent for publication of the case, dated: October 2023.

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