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DYNC1H1 in Spinal Muscular Atrophy: Diagnostic Findings From Two Families and a Comprehensive Review of Its Role in Neuromuscular and Neurodevelopmental Disorders

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ABSTRACT

Background: *DYNC1H1* is a critical gene implicated in neurodevelopmental and neuromuscular disorders with overlapping and variable phenotypes that challenge diagnosis.

Methods and Results: Whole exome sequencing in patients presenting with motor neuron disease symptoms and a predominant pattern of lower-limb muscle weakness revealed pathogenic *DYNC1H1* variants. This expands the known phenotypic spectrum to include rare features such as scapular winging and camptocormia. Clinical evaluations of affected individuals revealed features consistent with SMA-LED, reinforcing the role of *DYNC1H1* in neuromuscular disorders. A review of 208 published *DYNC1H1* variants highlighted significant clustering in the tail domain, primarily associated with neuromuscular conditions like SMA-LED. Approximately 28% of variants exhibited overlapping neuromuscular and neurodevelopmental features, emphasizing the diagnostic challenges posed by phenotypic overlap. These findings underscore the necessity of comprehensive clinical and genetic evaluations to address the variability observed within families and improve genotype–phenotype correlations.

Conclusion: This study reinforces the importance of *DYNC1H1* in motor neuron function and its pivotal role in neurodevelopmental and neuromuscular disease mechanisms. The integration of exome sequencing in clinical practice is essential for identifying rare and novel variants, enhancing diagnostic accuracy. We recommend incorporating *DYNC1H1* screening into diagnostic workflows to advance understanding and management of conditions with overlapping phenotypes.

1 | Introduction

Spinal muscular atrophies (SMAs) represent a clinically and genetically heterogeneous group of inherited motor neuropathies characterized by degeneration and loss of motor neurons in the anterior horn of the spinal cord. This neuronal degeneration results in varying degrees of muscle weakness, and in severe cases, leads to respiratory failure and early mortality. While the majority of SMA cases are caused by homozygous deletions of the *SMN1* (OMIM#600354) on chromosome 5q (de Rezen Pinto et al. 2021; Schiavo et al. 2013), a subset of cases arises from variants in genes outside the 5q locus, collectively referred to as non-5q SMA. Recent advances in genetic sequencing technologies, particularly massively parallel sequencing, have facilitated the identification of non-5q SMA-associated genes. Among these, pathogenic variants in *DYNC1H1* (Dynein cytoplasmic 1 heavy chain 1 gene) (OMIM#600112) have emerged as a significant contributor to autosomal dominant SMA (Theuriet et al. 2023).

The *DYNC1H1*, located on chromosome 14q32 and comprising 78 exons (Chan et al. 2018), encodes a large protein integral to intracellular processes, including cargo transport, axonal transport, regulation of the Golgi apparatus, organelle motility, spindle-pole organization, and nuclear migration during mitosis (Trimouille et al. 2018; Li et al. 2021; Amabile et al. 2020). Functionally, the DYNC1H1 protein is organized into four major domains: the tail domains, linker domain, motor domains, and microtubule-binding or stalk domain (Becker et al. 2020).

Variants within these domains disrupt critical molecular functions, giving rise to a diverse spectrum of neuromuscular and neurodevelopmental phenotypes collectively classified as *DYNC1H1*-related disorder. Neuromuscular presentations include autosomal dominant SMA with lower extremity predominance (SMA-LED; OMIM#158600) and Charcot–Marie-Tooth type 2O (CMT2O; OMIM#614228). Neurodevelopmental manifestations encompass malformations of cortical development (MCD; OMIM#614563) and a distinct epilepsy phenotype, which may occur as the sole clinical presentation, without any neuromuscular involvement. Epilepsy is a particularly prominent feature, ranging from isolated seizure disorders to severe forms such as developmental and epileptic encephalopathy, including infantile epileptic spasms syndrome (Möller et al. 1993). Patients with neurodevelopmental involvement often present with intellectual disability, developmental delay, and seizures, with epilepsy emerging as the most frequently reported feature. Notably, Møller et al. demonstrated that approximately 40% of individuals harboring *DYNC1H1* variants exhibit epilepsy, underscoring its significant prevalence and clinical relevance (Möller et al. 1993).

Many patients display overlapping features of neuromuscular and neurodevelopmental disorders, reflecting the complex and multifaceted nature of *DYNC1H1*-related conditions (Amabile et al. 2020; Becker et al. 2020; Möller et al. 2024). Recent studies, including the largest published cohort to date, have demonstrated that pathogenic variants in *DYNC1H1* frequently result in phenotypes involving these overlapping features (Möller et al. 2024). Despite growing recognition of these patterns, the phenotypic and molecular spectrum of *DYNC1H1*-related disorders remain incompletely characterized.

Genotype–phenotype correlation studies, including investigations in murine models, have highlighted a relationship between variant location and clinical presentation. Specifically, variants located in the tail domains of *DYNC1H1* are predominantly associated with SMA-LED, the most common neuromuscular phenotype linked to this gene (Harms et al. 2010; Weedon et al. 2011; Antoniadi et al. 2015; Scoto et al. 2015; Maretina et al. 2019; Willemsen et al. 2012). SMA-LED typically presents at birth or early childhood with clinical features including pronounced lower limb weakness, muscle atrophy, and progressive motor impairment (Scoto et al. 2015; Zambon et al. 2023; Punetha et al. 2015). However, due to the overlapping clinical features of *DYNC1H1*-related conditions, establishing a definitive diagnosis is challenging and often requires advanced genetic testing such as whole-exome sequencing (WES).

This study aims to contribute to the current understanding of *DYNC1H1*-related SMA-LED by presenting novel findings from two unrelated families with a dominantly inherited SMA-LED phenotype. The results are discussed in the context of previously reported cases, providing insights into the phenotypic and molecular spectrum of *DYNC1H1*-related disorders and emphasizing the importance of genetic testing in diagnosing rare neuromuscular diseases.

2 | Materials and Methods

2.1 | Ethical Compliance

Prior to participation, all individuals received appropriate genetic counseling, and informed consent was obtained from patients and/or their parents in accordance with the Declaration of Helsinki. Ethical approval was granted by the local institutional Ethics Committee at the Endocrinology and Metabolism Research Institute, Tehran University of Medical Science (IR.TUMS.EMRI.REC.1402.018).

2.2 | Clinical Evaluation

This study included two unrelated Iranian families presenting with dominantly inherited spinal muscular atrophy with lower extremity predominance (SMA-LED).

Clinical evaluation of the affected individuals was conducted by a multidisciplinary team comprising experienced endocrinologists, neurologists, neuroradiologists, and pathologists. This comprehensive assessment included a detailed medical history review, physical examination, and systematic clinical workup. Electromyography (EMG) and nerve conduction velocity (NCV) studies were performed on all four patients to assess motor and sensory nerve function. Additionally, advanced neurophysiological studies, including sensory and motor neurography and concentric needle electromyography, were conducted to further characterize neuromuscular function in the affected individuals. Imaging studies were performed for Case 1 (VI-1) and Case 4 (IV-2), with all results evaluated by an experienced neuroradiologist. Muscle biopsy was obtained from Case 1 (VI-1) to examine histopathological changes associated with the disease. These comprehensive clinical and neurophysiological evaluations provided essential insights into the phenotypic manifestations and neuromuscular abnormalities associated with the identified variants.

2.3 | Molecular Genetic Assessments

Peripheral blood samples were collected from affected individuals and their immediate family members. DNA was extracted using standard protocols. WES was performed on DNA from two affected individuals, VI-1 from family 1 and V-2 from family 2.

The variants identified through WES were validated by bidirectional Sanger sequencing, which was also used for segregation analysis within the families. DNA samples from the probands, their affected mothers, and their unaffected fathers were analyzed to confirm co-segregation of the identified variants with the disease phenotype.

To assess evolutionary conservation, multiple sequence alignments of the DYNC1H1 protein across various species were performed using COBALT (Constraint-Based Multiple Alignment Tool) and visualized with the Jalview tool. The high conservation of the identified variants supported their potential pathogenicity.

2.4 | Variant Identification and Analysis

To identify reported variants in the *DYNC1H1*, a systematic search was conducted in the PubMed database (https://pubmed.ncbi.nlm.nih.gov/) using the keyword "DYNC1H1". The search covered publications between 1993 and 2024 and yielded 192 articles. After an initial review, articles that were irrelevant to the scope of this study were excluded. Articles reporting *DYNC1H1* variants associated with cancers were also excluded due to their lack of relevance to neuromuscular or neurodevelopmental disorders. Additionally, relevant articles not captured in the PubMed search were identified through cross-referencing within reviewed reports. Synonymous variants were excluded from all searches to focus on pathogenic and potentially disease-associated variants. A summary of the reviewed literature and the associated variants is presented in Table S1.

Further pathogenicity assessment of *DYNC1H1* variants was performed using the Franklin platform (https://franklin.genoox.com). Franklin integrates data from publicly available population, disease, and sequence databases, as well as published literature, to evaluate variants based on ACMG guidelines. The platform employs artificial intelligence to prioritize pathogenic variants. A total of 208 variants were analyzed, and correlations between genotype and phenotype were examined in detail. Table S1 provides an overview of the pathogenicity assessments, while the detailed genotype–phenotype correlations are illustrated throughout the study.

3 | Results

3.1 | Clinical Features

3.1.1 | Family 1

3.1.1.1 | Case 1 (VI-1). The proband, an 11-year-old girl born to consanguineous parents (Figure 1A), presented with a history of toe walking and progressive proximal and distal muscle weakness in the lower limbs since the age of 3. The weakness, which did not affect the upper limbs, showed slow progression. She underwent Achilles tendon surgeries at ages 2 and 5 due to contractures. Her medical history included cardiac issues and pancreatitis, but she had no sensory, bladder, or bowel dysfunction. Bulbar and facial functions were preserved, and there was no evidence of muscle cramping or fasciculations. Despite borderline intelligence quotient (IQ) and attention-deficit/hyperactivity disorder (ADHD; OMIM#143465) treated with methylphenidate, her developmental progress was unremarkable.

Neurological examination revealed multiple musculoskeletal abnormalities, including camptocormia, mild scoliosis, lordosis, a waddling gait, and proximal muscle weakness in the lower limbs. Muscle strength in the neck and upper limbs was normal, while proximal and distal lower limb strength was reduced to 4/5. Deep tendon reflexes (DTR) were +1 in both upper and lower limbs, and plantar reflexes were negative. EMG indicated a neurogenic pattern in the lower limb muscles. A muscle biopsy from the left vastus lateralis revealed mild atrophic changes with predominance of type 1 fibers. The nerve biopsy showed no abnormalities. Brain MRI indicated mild lateral ventricular dilation, and creatine phosphokinase (CPK) levels were slightly elevated at 420 U/L.

3.1.1.2 | Case 2 (V-2). The proband's mother experienced a similar, although less severe, phenotype beginning in childhood. She reported difficulty climbing stairs and running, along with cramping in the lower limb muscles, which was absent in her daughter. She had no cardiac or mental health issues, and facial and cranial muscles were unaffected.

Neurological examination revealed proximal and distal weakness in the lower limbs, with muscle strength reduced to 4/5, while the upper limbs remained unaffected. Additional findings included increased lumbar lordosis, a positive Gower's sign, and difficulty walking on tiptoes and heels. DTRs were absent. EMG revealed a neurogenic pattern in all tested lower limb muscles. A muscle biopsy was not performed.

3.1.2 | Family 2

3.1.2.1 | Case 3 (V-2). The proband, a 9-year-old girl born to nonconsanguineous parents (Figure 1B), presented with proximal lower limb weakness, difficulty running, and an inability to sit up from a lying position, with symptoms beginning at age 7. There was no history of cramping, fasciculations, or developmental delays.

Neurological examination revealed a positive Gower's sign, mild scapular winging (more pronounced on the left), and proximal lower limb weakness (4/5), while distal lower limb and upper extremity strength were preserved (5/5). DTRs were +1 in the lower limbs and +2 in the upper limbs. The Babinski sign was negative, and sensation was intact. EMG indicated chronic denervation in the lower limb muscles, consistent with motor neuron disease. CPK levels were in the normal range (163 U/L).

3.1.2.2 | Case 4 (IV-2). The mother of Case 3, a 44-year-old woman from a consanguineous marriage (Figure 1B), presented with a history of slowly progressive proximal lower limb weakness, camptocormia, a waddling gait, and overriding toes on her right foot. These symptoms began in childhood and progressively worsened over time. Her upper limbs were notably strong with no abnormalities. Unlike her daughter, she experienced cramping and transient fasciculations in the lower limbs but had no bulbar symptoms, urinary dysfunction, or systemic

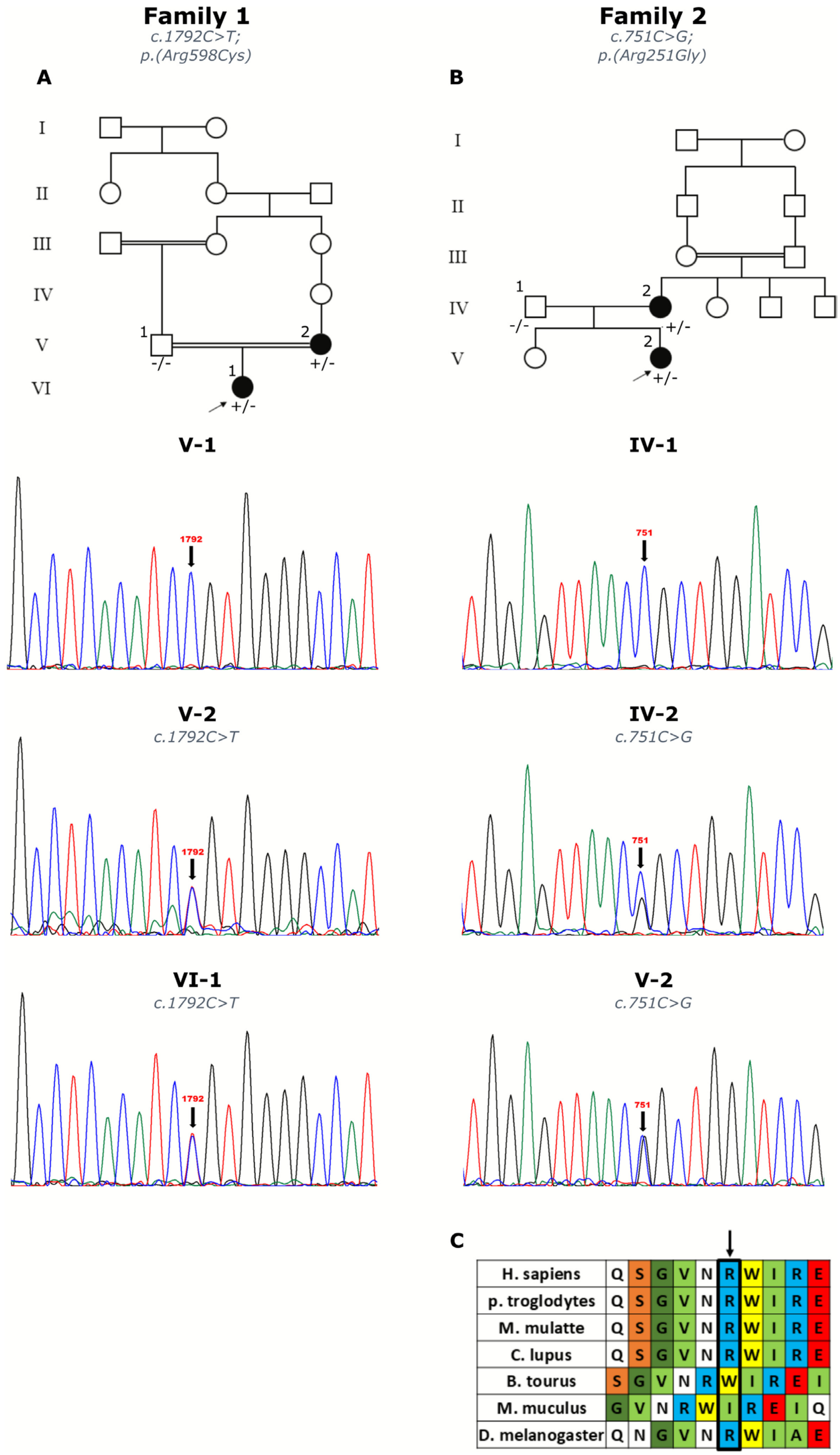

FIGURE 1 | Pedigrees, segregation results, and evolutionary conservation of *DYNC1H1* variant. (A, B) Pedigrees of the two identified families with *DYNC1H1*-related disorders. Affected individuals (filled symbols) are heterozygous for the *DYNC1H1* variants (+/−), with segregation confirmed in additional family members (− indicates the wild-type allele). Unaffected individuals are represented by open symbols. Squares represent males, circles represent females, and the proband in each family is marked with an arrow. Genotypes were determined through Sanger sequencing, with variant locations indicated by arrows in the chromatograms. (C) Evolutionary conservation of amino acids in DYNC1H1 orthologues at p. (Arg251) site, where a missense change was identified. The substitution affects an evolutionarily conserved residue, as indicated by the arrow.

involvement such as respiratory or cardiovascular disease. Additionally, she was unable to walk on tiptoe and had difficulty walking on her heels. She reported delayed motor development and a lifelong history of difficulty running and climbing stairs.

Neurological examination revealed intact mental status and cranial nerves, normal sensation in the arms and legs, a normal finger-to-nose test, and no scapular winging. There were no signs of atrophy or fasciculation in the tongue or limbs. However, she exhibited severe lordosis without rigidity. Muscle strength was 5/5 in the upper limbs, reduced to −4/5 in the proximal lower limbs, and 4/5 in the distal lower limbs. DTRs were absent in the lower limbs but +1 in the upper limbs. The Babinski sign was negative.

Nerve conduction studies demonstrated low amplitude in the tibial nerve response, while other parameters were normal. Electromyography revealed chronic denervation, more pronounced in proximal than distal lower limb muscles. Thigh MRI revealed fat infiltration in the vastus lateralis, vastus intermedius, and biceps femoris muscles, with relative sparing of the gastrocnemius muscles and no evidence of active inflammation. CPK levels were normal (131 U/L).

Given the neurogenic pattern observed in the muscles, particularly in the proximal lower limbs, genetic testing for 5q SMA was performed. Results were negative for homozygous deletion of *SMN1* exons 7 and 8.

All patients exhibited proximal muscle weakness, and in each family, one affected individual also presented with camptocormia, initially suggesting a myopathic process. However, electrodiagnostic evaluation revealed neurogenic motor unit action potentials, indicating a possible motor neuron disorder. Given the predominantly proximal distribution of weakness, SMA was considered in all investigated cases; nevertheless, no *SMN1* deletions were identified in Case 4. Consequently, whole exome sequencing was performed to investigate alternative genetic etiologies of motor neuron disease.

The clinical features observed in the probands and their affected mothers are summarized in Table 1.

3.2 | Genetic Findings

The WES data from Cases 1 and 3 were analyzed using Ingenuity Variant Analysis (IVA) software (Qiagen, Hilden, Germany), with a specific focus on autosomal-dominant inheritance in known neurogenetic disease-associated genes. The filtering process initially prioritized heterozygous coding variants, referencing the Human Genome Mutation Database (HGMD) and ClinVar variant databases. Variants predicted to be damaging or of uncertain impact were selected for further analysis. This approach identified two distinct heterozygous missense variants. In Family 1, Case 1 carried a variant, c.1792C>T (absent in gnomAD v4.1.0, ESP, and 1000 Genomes) in exon 8 (p. (Arg598Cys); NM_001376.5), located within the tail domain of *DYNC1H1*. In Case 1, we identified an additional heterozygous variant in *PNLIP* (NM_000936.4): c.900C>A, p. (Phe300Leu), currently classified as a variant of uncertain significance. However, given the role of *PNLIP* in pancreatic lipase function, the identified alteration may plausibly underlie the pancreatic abnormalities observed in this patient. In Family 2, the affected individual (Case 3) was found to harbor a different variant, c.751C>G (absent in gnomAD v4.10) in exon 4 (p. (Arg251Gly); NM_001376.5), also within the tail domain of *DYNC1H1*. Genetic analysis did not reveal any compound heterozygous or homozygous variants in other genes of clinical relevance.

Both variants were validated using polymerase chain reaction (PCR) followed by Sanger sequencing in the affected daughters and their mothers. Pedigree analysis confirmed an autosomal dominant inheritance pattern, aligning with the clinical presentations. Sequencing chromatograms revealed that the unaffected fathers were homozygous for the wild-type alleles, while the affected individuals carried heterozygous missense variants (Figure 1A,B). Given that the family members of the affected mothers were asymptomatic and in good health, genetic testing was not performed on any of them. Accordingly, the variants identified in the mothers are presumed to be of *de novo* origin.

The c.751C>G variant is a novel heterozygous missense variant in exon 4, impacting an evolutionarily conserved arginine residue. This variant has not been previously described in the literature or reported in association with any clinical cases. To assess the conservation of this residue, multiple sequence alignments of DYNC1H1 protein, including the arginine at position 251, were performed across several species using COBALT and the Jalview tool. These analyses demonstrated that arginine 251 is highly conserved and likely serves a functional role (Figure 1C).

4 | Discussion

This study contributes to the growing understanding of *DYNC1H1*-related neuromuscular disorders by providing a comprehensive review of all reported *DYNC1H1* variants and their clinical associations. Additionally, it reports four affected individuals from two unrelated families with pathogenic variants in the tail domain of *DYNC1H1*. The findings align with prior reports on SMA-LED and provide additional insights into the phenotypic and mutational spectrum of *DYNC1H1*-associated disorders (Wee et al. 2010), further broadening our understanding of these complex conditions.

The clinical presentation of the four patients was consistent with the classical SMA-LED phenotype, characterized by early childhood-onset lower limb weakness and wasting predominantly involving the proximal muscles. Notably, trunk weakness and camptocormia observed in two cases expand the known phenotypic spectrum, as these features are rarely reported in SMA-LED (Beecroft et al. 2017). One patient presented with neurodevelopmental features, including ADHD and borderline intellectual disability, further highlighting the variability in *DYNC1H1*-associated disorders. These findings underscore the overlapping features of neuromuscular and neurodevelopmental phenotypes linked to *DYNC1H1* (Theuriet et al. 2023; Chan et al. 2018; Li et al. 2021; Beecroft et al. 2017; Scoto et al. 2015).

A review of 208 reported *DYNC1H1* variants provides valuable context for interpreting genotype–phenotype correlations.

TABLE 1 | Features of our reported probands and their affected mothers.

Patient	VI-1 (Family 1, Case1)	V-2 (Family 1, Case2)	V-2 (Family 2, Case3)	IV-2 (Family 2, Case4)
Sex	Female	Female	Female	Female
Onset age	3 Years	Childhood	2 Years	Childhood
Age at examinations	11 Years	51 Years	9 Years	44 Years
Family history	+/ consanguineous parents	−/ nonconsanguineous parents	−/ nonconsanguineous parents	+/ consanguineous parents
Muscle weakness	LL prox > dist	LL prox > dist	LL prox	LLprox > dist
DTR	+UL, +LL	−UL, −LL	++UL, +LL	−UL, −LL
Developmental delay	Unremarkable	Unremarkable	Unremarkable	+
Intellectual ability	Borderline IQ	Normal	Normal	Normal
Creatine kinase level	420	NA	163	131
MRI of the lower limb findings	Not done	Not done	Not done	Fat infiltration in VL, VI, BF, GM, GL
EMG findings	Neurogenic pattern in lower limb	Neurogenic pattern in lower limb	Neurogenic pattern in lower limb	Neurogenic pattern in lower limb
Brain MRI findings	Mild lateral ventricular dilation	Not done	Not done	Not done
Muscle biopsy findings	Slight atrophic changes with type 1 uniformity and predominancy	Not done	Not done	Not done
Skeletal deformities	Camptocormia and mild scoliosis and lordosis, Achilles and knee contracture	Lordosis, Achilles contracture	Mild asymmetric scapular winging in both sides, mild lordosis	Camptocormia, overriding fingers, lordosis
Seizures	–	–	–	–
Variant	c.1792C>T	c.1792C>T	c.751C>G	c.751C>G
Protein	p. Arg598Cys	p. Arg598Cys	p. Arg251Gly	p. Arg251Gly
Others	ADHD/cardiac problems and pancreatitis	Fasciculation and cramp	–	Fasciculation and cramp

These variants are distributed across the tail, motor, stalk, and linker domains, with 54% located in the tail domain despite its smaller coding size. In contrast, 25% of variants are found in the motor domain, 13% in the stalk domain, and 8% in the linker domain (Figure 2). This clustering of variants in the tail domain highlights its critical role in neuronal cargo transport and motor neuron function (Peeters et al. 2015; Harms et al. 2012; Fiorillo et al. 2014). Variants in this region are predominantly associated with neuromuscular disorders such as SMA-LED and CMT. In contrast, variants in the motor and stalk domains are more frequently linked to NDDs, such as intellectual disability and epilepsy (Li et al. 2021; Scoto et al. 2015; Peeters et al. 2015). These domain-specific trends reinforce the importance of variant location in determining clinical outcomes.

Both variants identified in this study—c.1792C>T; p. (Arg598Cys) and c.751C>G; p. (Arg251Gly)—were located in the tail domain. The p. (Arg598Cys) variant is one of the most frequently reported pathogenic variants in *DYNC1H1* and is primarily associated with SMA-LED, although it has occasionally been linked to CMT (Li et al. 2021; Punetha et al. 2015; Beecroft et al. 2017; Scoto et al. 2015; Peeters et al. 2015; Strickland et al. 2015). The clinical presentation of our patients carrying the p. (Arg598Cys) variant aligns with previously reported cases, notably in features such as early-onset, lower-limb-predominant weakness, delayed motor milestones, and Achilles tendon contractures. However, neither individual in our cohort exhibited cognitive impairment, epilepsy, or generalized arthrogryposis, which have been described in other affected cohorts. Additionally, the mild elevation of CPK and subtle ventricular dilatation observed on brain MRI in the daughter (VI-1) represents potentially novel findings. These comparisons highlight both the recurring core phenotype associated with p. (Arg598Cys) and the phenotypic variability that can occur within a single family. Collectively, our observations reinforce the characteristic clinical features of this variant while contributing new insights into its intra-familial and broader clinical heterogeneity. Furthermore, this suggests that specific variants within the tail domain may have pleiotropic effects, influencing both axonal integrity and motor neuron function.

The novel p. (Arg251Gly) variant adds to the mutational spectrum of *DYNC1H1* and supports the pathogenic significance of codon 251, where another substitution (p. (Arg251Cys)) has been reported in several studies (Theuriet et al. 2023; Chan et al. 2018; Li et al. 2021; Amabile et al. 2020). The higher prevalence of neuromuscular phenotypes associated with tail domain variants supports the hypothesis that disruption in cargo transport mechanisms primarily affects long motor neurons innervating the lower extremities (Becker et al. 2020).

Among the reviewed *DYNC1H1* variants, 29% are linked to neuromuscular disorders, 43% to neurodevelopmental features, and 28% to overlapping phenotypes, reflecting the broad

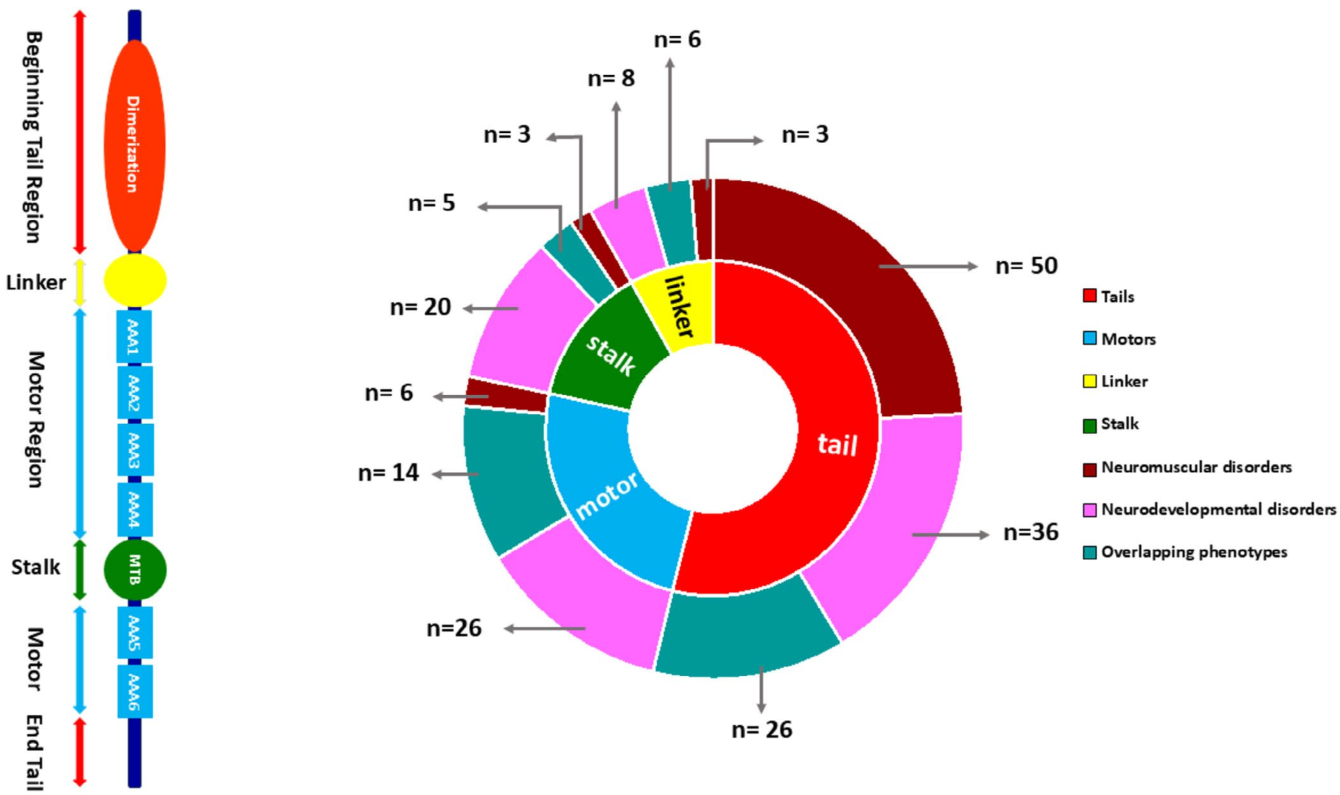

FIGURE 2 | Distribution of previously published *DYNC1H1* variants. The Pie chart illustrating the distribution of 208 published *DYNC1H1* variants (n: Number of variants) across the functional domains of the DYNC1H1 protein: Tail (light red), motor (blue), linker (yellow), and stalk (green). The chart also highlights the prevalence of different phenotypes associated with *DYNC1H1* variants within each domain, including neuromuscular disorders (dark red), neurodevelopmental disorders (pink), and overlapping phenotypes (teal). Multiple phenotypes in *DYNC1H1*-related disorders are indicated as overlapping phenotypes. On the left, a schematic representation of the DYNC1H1 protein structure indicating the tail, motor, linker, and stalk domains.

functional impact of these variants. Within the neuromuscular disorder category, SMA-LED was the most frequently reported phenotype, accounting for 41 cases (68%), followed by CMT disease with 15 cases (25%), as distinctly documented in the literature (Figures 3 and 4).

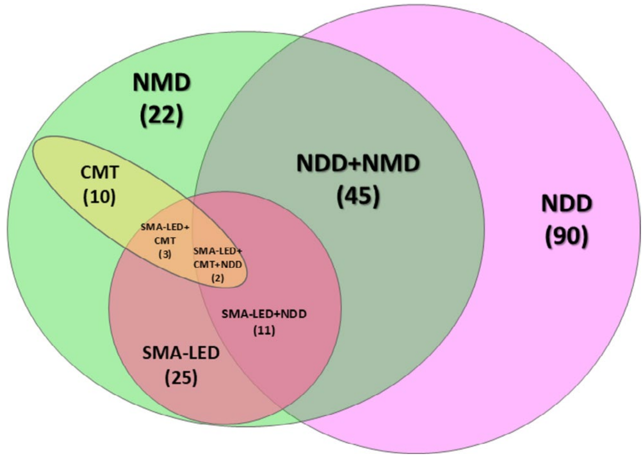

FIGURE 3 | Prevalence of phenotypes associated with *DYNC1H1* variants. The Venn diagram illustrates the distribution and overlap of phenotypes reported in *DYNC1H1*-related disorders, specifically neuromuscular disorders (NMD) and neurodevelopmental disorders (NDD). Overlapping regions display shared phenotypic features between these categories, reflecting the complex genotype–phenotype relationships. Specific conditions, including Spinal Muscular Atrophy with Lower Extremity Predominance (SMA-LED) and Charcot–Marie–Tooth Disease (CMT), are indicated, demonstrating their association with the diverse phenotypic spectrum of *DYNC1H1* variants.

The substantial proportion of variants exhibiting overlapping neuromuscular and neurodevelopmental phenotypes complicates genotype–phenotype correlations and underscores the challenges in diagnosis (Chan et al. 2018; Amabile et al. 2020; Beecroft et al. 2017; Mei et al. 2023). Additionally, phenotypic variability, even within families carrying the same variant, further contributes to these complexities (Tsurusaki et al. 2012; Viollet et al. 2020). For instance, while SMA-LED patients typically present with lower limb-predominant weakness, rare features such as scapular winging and trunk muscle involvement, as observed in this study, expand the phenotypic spectrum (Theuriet et al. 2023; Beecroft et al. 2017). Muscle biopsy findings in Case 1, showing type I fiber predominance with uniformity, a feature more commonly associated with congenital myopathies than motor neuron diseases, highlight the overlap between different neuromuscular conditions. These observations underscore the importance of genetic testing and comprehensive clinical evaluations to accurately delineate *DYNC1H1*-related disorders and resolve diagnostic ambiguities (Chan et al. 2018; Amabile et al. 2020; Beecroft et al. 2017; Mei et al. 2023).

Advanced diagnostic tools, including WES, muscle MRI, and EMG, are invaluable in delineating overlapping phenotypes and identifying causative variants. For instance, although SMA-LED and CMT share overlapping clinical presentations, their

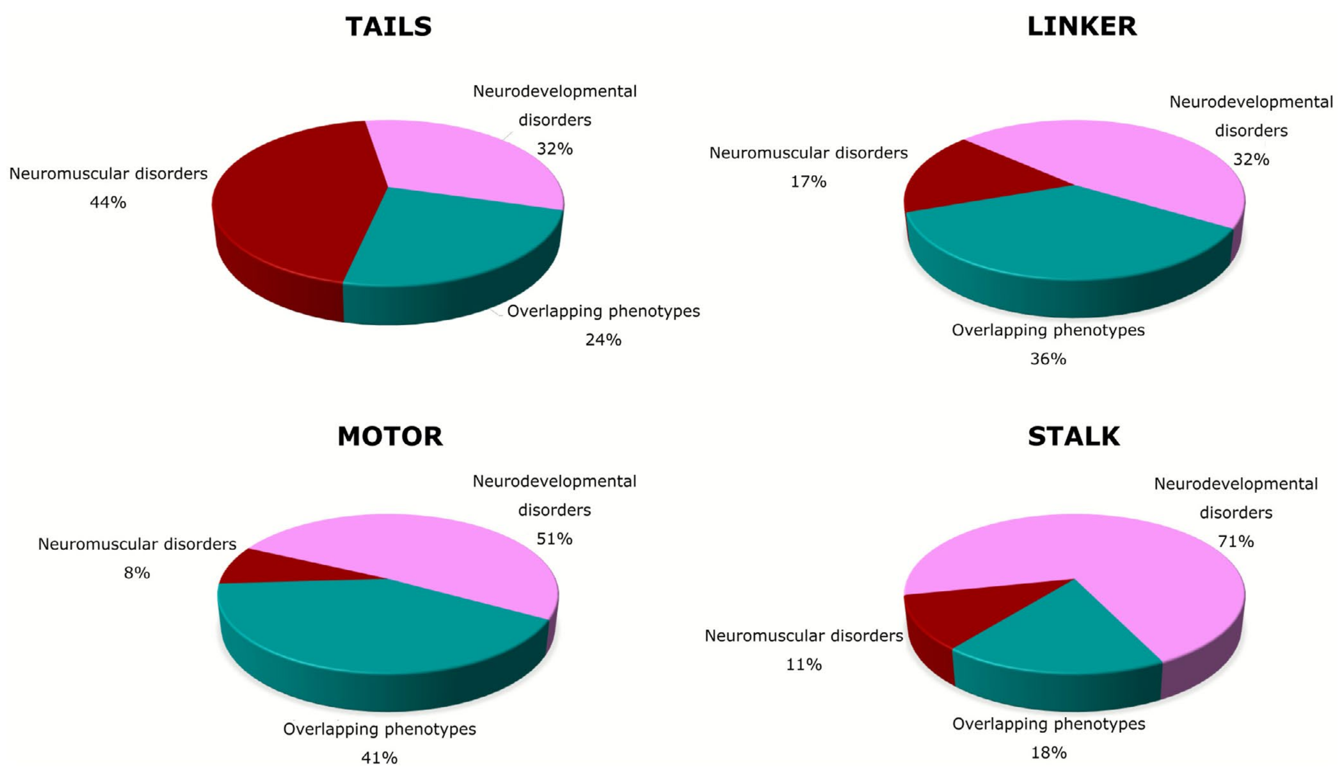

FIGURE 4 | Distribution of phenotypes within functional domains of DYNC1H1. Circle diagram illustrating the distribution of various phenotypes associated with *DYNC1H1* variants across each functional domain of the DYNC1H1 protein (tail, motor, linker, and stalk) in percent. Color coding corresponds to Figure 2, distinguishing neuromuscular disorders (NMD), neurodevelopmental disorders (NDD), and overlapping phenotypes. The overlapping phenotypes emphasize the functional complexity and diverse clinical manifestations resulting from *DYNC1H1* variants in these domains.

EMG findings offer a key diagnostic distinction. In SMA-LED, EMG typically reveals motor axonal involvement or motor neuron loss, whereas in CMT, it reveals a pattern of both motor and sensory nerve involvement, facilitating differentiation between the two conditions (Li et al. 2021; Amabile et al. 2020; Zambon et al. 2023; Mei et al. 2023). The identification of pathogenic *DYNC1H1* variants, including the novel p. (Arg251Gly) variant, emphasizes the utility of genetic testing in resolving diagnostic ambiguity and enabling precise sub-classification of *DYNC1H1*-related disorders.

5 | Conclusions

In conclusion, our review of *DYNC1H1* variants supports the growing evidence for domain-specific genotype–phenotype correlations. Specifically, variants in the tail domain are predominantly associated with neuromuscular disorders, while those in the motor domain are more commonly associated with neurodevelopmental conditions. All patients in our cohort carry tail domain variants and exhibit features of SMA-LED, aligning with this domain-specific pattern. Furthermore, the identification of a novel pathogenic variant and rare clinical features expands the phenotypic spectrum of *DYNC1H1*-related disorders and underscores the importance of protein domain architecture in shaping clinical outcomes.

The study underscores the importance of comprehensive clinical, pathological, and genetic evaluations, with WES being critical for accurate diagnosis. As *DYNC1H1* is implicated in various neurodevelopmental and neuromuscular conditions, including intellectual disabilities, cortical malformations, autism, spastic tetraplegia, and motor neuron diseases, it should be prioritized in diagnostic workflows. Future research should focus on the molecular mechanisms and genotype–phenotype correlations to enhance diagnostic precision and guide therapeutic strategies (Amabile et al. 2020; Mei et al. 2023; Fernández-Eulate et al. 2023; Carter et al. 2019).

Author Contributions

M.N. and M.S. contributed to the conception and design of the study, collected the data and drafting the manuscript. M.S., A.B., S.F. and N.N. contributed to analysis and interpretation of data. B.A., K.B. and E.S.A. recruited the patients and collected/interpreted clinical information. M.M.A. contributed to establishing the research framework and drafting the manuscript. H.T. contributed to acquisition of data and writing-review and editing. All authors provided critical revisions and approved the final manuscript.

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding authors upon reasonable request.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Appendix S1:** mgg370163-sup-0001-Supinfo1.docx.