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REVIEW

DIFFERENTIATION OF DISTAL MYOPATHIES USING MUSCULAR MAGNETIC RESONANCE IMAGING: A SYSTEMATIC REVIEW

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ABSTRACT

Objectives: Diagnosis of distal myopathies is challenging. Muscle magnetic resonance imaging (MRI) is an increasingly recognized tool for diagnosis and follow-up of muscle diseases. Given the rarity of these diseases, the unique MRI pattern of their muscle involvement remains unclear.

Materials and methods: We conducted a comprehensive search in PubMed, Scopus, and Google Scholar Library to identify English-language case reports and case series studies of different myopathies published between January 2000 and September 2024. The type of gene mutation in patients, their MRI findings, including regions imaged, muscles involved and spared, and the Mercuri scoring system for assessing the fat infiltration, were extracted from the studies.

Results: Thirty-four studies consisting of 6 mutations were analyzed. The tibialis anterior was the most severely compromised muscle in myosin heavy chain-7 (*MYH7*), titin (*TTN*), glucosamine (UDP-N-acetyl)-2-epimerase/N-acetylmannosamine kinase (*GNE*), and dysferlin (*DYSF*) mutations. Extensor digitorum was in second place in TTN-associated myopathy. Hamstring muscles and gastrocnemius medial heads were moderately affected in *GNE* and *DYSF* cases, while vastus muscles and calf muscles were severely involved in adenylosuccinate synthase 1-related myopathies (*ADSSL1*). In matrin-3 (*MATR3*) mutation cases, the gastrocnemius and semimembranous muscles had the most pronounced fat infiltration.

Conclusion: We defined unique patterns for different myopathies that can be implemented in the initial clinical assessment of patients with distal myopathy. We advise further studies with a larger number of patients.

KEYWORDS

Distal myopathy, magnetic resonance imaging, MRI scan, mutation, myopathy

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INTRODUCTION

Distal myopathies are a heterogeneous group of hereditary disorders characterized by predominant weakness in the feet and/or hands[1]. With advancements in genetic studies, over twenty genes have been identified as being associated with distal myopathies, although many of these disorders still lack genetic characterization[2]. Mutations in various group of muscle proteins, including desmin[3], nebulin[4], dysferlin (*DYSF*)[5], titin (*TTN*)[6], myosin heavy chain (*MYH*)[7], glucosamine (UDP- N-acetyl)-2-epimerase/ N-acetylmannosamine kinase (*GNE*)[8,9], and myotilin[10], have been linked to distal myopathies. Six traditional distal myopathies are commonly referred to by eponyms: Welander, Udd, Markesbery, Nonaka, Miyoshi, and Laing[11].

Dominant distal myopathies, such as Welander distal myopathy and Tibial muscular dystrophy (Udd myopathy), are more prevalent in Sweden and Finland. In contrast, recessive *GNE* myopathy has a higher prevalence in East Asia and the Middle East[12-14].

The diagnosis of distal myopathies often remains challenging due to their clinical and genetic heterogeneity, as well as clinical overlap among different mutations[15,16]. A definitive diagnosis can be made by identifying the underlying genetic defect[16,17]. However, due to the size and complexity of the involved muscle genes, comprehensive molecular analysis is limited to specialized genetic centers, and it takes considerable time to yield results[18]. Therefore, it is important to use additional diagnostic tools to achieve a clinical diagnosis and target gene analysis. Complementary tests such as serum creatine kinase levels, electrodiagnostic studies, and muscle biopsy are not sufficiently specific, further complicating the diagnostic process[19].

Magnetic resonance imaging (MRI) offers high-resolution anatomical visualization of skeletal muscles, providing excellent contrast between soft tissues and allowing for the examination of individual muscles in sharp contrast to adjacent fat[19,20]. MRI can demonstrate valuable diagnostic changes such as selective muscle degeneration, fatty infiltration, and macroscopic changes in muscle size[21]. Although these changes are disease-nonspecific, the involvement of particular muscles may be characteristic of certain muscle diseases[22]. Additionally, an MRI scan is repeatable, non-invasive, and non-radiating, making it an ideal tool for clinical research and longitudinal studies[19,20].

MRI is increasingly used in the diagnostic workup of muscle diseases, quantification of disease progression, and the assessment of therapeutic response[19,21]. Its utility has been well demonstrated in studies of various neuromuscular diseases, including myopathies[23,24], lower motor neuron disorders[25], and myositis[26]. Importantly, MRI has a dual role in diagnosis, as it can guide biopsies and refine the selection of candidate genes for genetic analysis based on the pattern of muscle involvement[18,21].

However, most studies have only described MRI patterns in single-cohort groups of patients and lacked control groups representing other diseases. As a result, the diagnostic value of MRI in differentiating among various types of distal myopathies remains underexplored. The few studies that have assessed this aspect showed varying results depending on the type of disease[18].

This study aims to create a unique systematic review for the early diagnosis of inherited distal myopathies based on MRI findings, relying on specific patterns of affected muscles. The results can be used by physicians to establish diagnoses based on the recognition of MRI patterns, providing useful clues to guide genetic testing.

MATERIAL AND METHODS

This systematic review was conducted in accordance with the PRISMA-P 2015 Checklist[27]. In this systematic review, MRI data from all patients diagnosed with distal myopathy were collected, summarized, and evaluated. The local ethics committee of Tehran University of Medical Sciences approved the protocol of the study (protocol ID: IR.TUMS.SHARIATI.REC.1403.090). The study was also registered in the International Prospective Register of Systematic Reviews (PROSPERO) under the PROSPERO registration number CRD42022367806.

Search strategy: Relevant literature was identified through comprehensive searches of PubMed, Google Scholar, and Scopus for all English-language articles published between January 2000 and April 2022 relating to magnetic resonance imaging in distal myopathy patients. The search was updated in September 2024. Articles published before 2000 were excluded due to limitations in genetic testing. No advanced search filters or limits were used in PubMed to ensure no articles were missed. In contrast, Google Scholar searches were limited to articles with search terms appearing in the title, due to its broader indexing scope. The search terms were based on two key concepts: distal myopathy ("distal myopathies," "distal muscular dystrophy") and MRI ("magnetic resonance imaging," "magnetic resonance spectroscopy," "MRS").

Inclusion/exclusion criteria

As inherited distal myopathies are rare, eligible articles were limited to case reports and case series. References cited in review articles were also included. No published articles were excluded based on design alone. There were no restrictions regarding age, gender, race, or geographic region. Only studies with genetically confirmed cases were considered. Non-English articles were excluded due to limitations in extracting data. We selected six mutations that were most commonly reported across the included studies and had sufficient sample sizes and consistent MRI data. This made it possible to compare the patterns of muscle involvement with greater accuracy.

Data extraction and synthesis

Data extraction was performed independently by two

review authors to identify those potentially meeting the inclusion criteria. Disagreements were resolved through discussion, and if consensus could not be reached, a third reviewer was consulted. Information extracted from the articles included the type of gene mutation, and their MRI findings, including regions imaged, muscles involved and spared, and the scoring system used to assess fat infiltration. Typically, the combined protocols of T1-weighted and short-tau inversion recovery (STIR) are used in MRI. MRI protocols typically included both T1-weighted and short-tau inversion recovery (STIR) sequences. T1 images show muscle anatomy, fat replacement indicating severe damage, and muscle loss identified by increased signal intensity and muscle mass to identify atrophy or hypertrophy. Progressive muscle wasting, with increasing edema, can be identified in T2 or STIR images, which appear as areas of increased signal intensity. To assess the mean fat infiltration of muscles in MRI scans, a modified Mercuri scale was utilized[28]. This scale classifies muscle fat infiltration as follows:

Score 0: Normal appearance.

Score 1: Early fat infiltration, scattered areas of T1 high signal.

Score 2: Numerous discrete areas of T1 high signal with beginning confluence <30% of muscle volume.

Score 3: Fatty infiltration of 30-60% of muscle volume.

Score 4: Fatty infiltration of >60% of muscle volume[29].

Risk of bias assessment

Due to limitations in case series and case report studies, there was no standard method to assess the quality of these articles. Previous studies employed two approaches for this purpose: assessment by two experts in the field based on their clinical experience, or using a consensus-based clinical case reporting guideline. In this study, the CARE guideline was used[30].

Data analysis

Statistical significance for all tests was calculated based on a two-tailed alpha level of 0.05. For each significant p-value, eta-squared or r-squared was calculated to determine effect size, as appropriate. The Mann–Whitney U test was used to compare different myopathies, and the Wilcoxon signed-rank test was used to analyze specific anatomical parts involved. Qualitative data were described using charts based on Mercuri grades, and quantitative variables were described using means and standard deviations.

RESULTS

A total of 2,067 studies were identified through searching databases. The number of 499 studies was removed due to duplication. Among the remaining studies, 334 were eligible for screening. Of these, 207 were excluded because they were irrelevant to the aims of this study. Among the 207 excluded studies, 18 were conference abstracts, and the

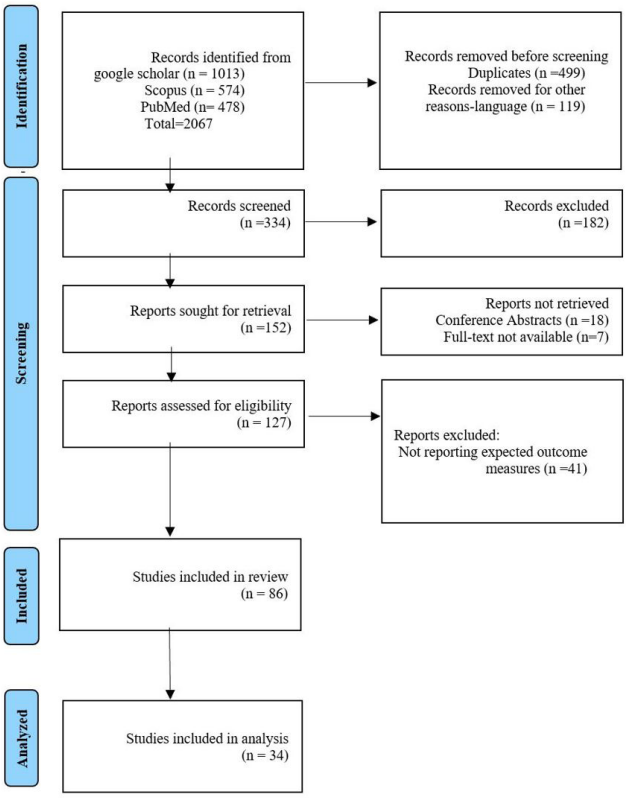


Figure 1. *PRISMA diagram of screening.*

full texts of 7 studies were not available despite contacting the corresponding authors by email. Finally, 127 studies were evaluated for eligibility. Following full-text review, 86 studies were included, and data from 34 of these were used for analysis *(Fig. 1)*.

Mutations in more than 25 genes have been introduced to be in correlation with distal myopathies in studies. The most prevalent genes were myosin heavy chain7 (*MYH7*), accounting for 98 cases, *DYSF* for 52 cases, matrin-3 (*MATR3*), *GNE*, adenylosuccinate synthase 1 (*ADSSL1*), and *TTN* for 40, 29, 21, and 16 cases, respectively *(Table 1)*. In this study, we mainly discuss the most prevalent and well-documented mutations and their compatible myopathies.

Table 2 describes the patterns of muscular involvement by different mutations in the upper limbs. *MYH7* gene mutations were found to mildly involve the deltoid, trapezius, triceps, and biceps brachii, with a mean muscle involvement of less than 10% across studies. *TTN* and *GNE* shared a similar pattern of muscle involvement, with moderate (10-30%) involvement of the posterior and anterior forearm muscles, and less than 10% of the deltoid, trapezius, and triceps were involved across studies for these genes.

Additionally, studies reported that patients with mutations in the *DYSF* gene had less than 10% involvement of the deltoid, infraspinatus, supraspinatus, triceps, brachialis, biceps brachii, and anterior forearm muscles. These myopathies were reported to cause only early fat infiltration (Mercuri score of 1) in the previously mentioned muscles, as observed in MRI sequences. However, studies focusing

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Mutation	Age	Sex ratio M/F	No of cases
ANO5	56.8 (44-73)	7/1	8
ACTN2	48.3 (34-68)	3/3	6
CAV3	17.2 (2-28)	2/4	6
MYH7	50.1 (7-72)	46/52	98
COL12A	24.0 (3-62)	5/1	6
PTRF	3	1/0	1
TTN	37.5 (16.88)	5/7	16
TIA1 + MYH7	64 (59-67)	0/3	3
TIA1	55.4 (48-63)	1/3	4
GNE	35.6 (26-46)	10/19	29
MATR3	55.5 (40-70)	19/21	40
ADSSL1	32.1 (27-39)	10/11	21
FHL1	14.2 (4-32)	1/5	6
DYSF	18.7 (3-40)	35/17	52
DNAJB6	48.2 (35-75)	12/0	12
ZASP	44.3 (41-48)	1/2	3
FLNC	40.0 (37-45)	4/0	4
NEB	18.0 (6-26)	2/1	3
HSPB1	44.7 (40-57)	7/2	9
FKRP	40.2 (21-64)	---	11
PESM	---	---	1
TTID	---	1/8	9
HNRNPA	---	5/3	8
CRYAB	70-74	2/0	2
VCP	---	---	1
KLHL9	---	0/1	1

Table 1. *Baseline characteristics of patients extracted (all) and included (in gray).*

on *MATR3* and *ADSSL1* did not report any upper extremity muscle involvement *(Tables 2 and 4)*.

Evaluation of lower extremity involvement in MRI scans yielded several notable findings *(Table 3)*. Studies reported that mutations in *MYH7* can affect all muscles of the lower extremities, though the degree of involvement varied. The tibialis anterior (TA) showed the highest level of muscle involvement in these gene mutations, with a mean range of 30–40%. Following that, the vastus muscles and extensor digitorum were the most widely affected, with 10–20% involvement. All other muscles were reported to have less than 10% involvement.

Regarding *TTN* gene mutations, the tibialis anterior was also reported to be severely involved, with over 40% of the muscle affected across all studies *(Table 3)*, corresponding to a Mercuri score of 3 *(Table 4)*. The extensor digitorum ranked second, with moderate (30-40%) involvement and a Mercuri score of 2 *(Tables 3 and 4)*. Additionally, 20–30% of the gluteus medius, hamstring muscles (semimembranosus, semitendinosus, and short and long heads of the biceps femoris), soleus, and peroneus were involved in TTN mutations. The gluteus maximus, adductor muscles, vastus intermedius, gracilis, sartorius, iliopsoas, medial head of the gastrocnemius, and popliteus were spared in our analysis (score 0) *(Tables 3 and 4)*.

For *GNE* mutations, the tibialis anterior also exhibited the highest rate of muscle involvement (more than 40%) with a Mercuri score of 3. Moderate involvement (score 2) was noted in the hamstring muscles (excluding the short head of the biceps femoris) and the medial gastrocnemius. The tensor fasciae latae, vastus medialis, lateralis, intermedius, and popliteus showed complete sparing (score 0) *(Tables 3 and 4)*.

Regarding *MATR3*, the most preferential involvement was observed in the medial and lateral gastrocnemius (more than 40%, score 3), followed by the soleus and semimembranosus muscles with average involvement of 30-40%. The gluteus minimus, iliopsoas, and tibialis anterior showed 20-30% involvement. The gracilis was spared in our evaluated studies (score 0) *(Tables 3 and 4).*

ADSSL1 mutations were associated with severe involvement of the vastus muscles and posterior leg compartment muscles (gastrocnemius and soleus), each assigned a Mercuri score of 3. Only 10-20% of the gracilis, sartorius, short head of the biceps femoris, tibialis anterior and posterior, extensor digitorum, and popliteus were involved (score 1). The gluteus muscles and iliopsoas tended to be spared (score 0) *(Tables 3 and 4)*.

In DYSF mutations, the tibialis anterior was the most extensively involved muscle (30-40%, score 3). The gastrocnemius was in second place, with 20-30% involvement. The gracilis, sartorius, and vastus lateralis showed complete sparing (score 0) *(Tables 3 and 4)*.

In cases with semimembranosus involvement, the MATR3 mutation exhibited significantly greater involvement compared to *TTN* mutations ($p = 0.019$). TTN mutations were observed to affect the short head of the biceps femoris more severely than *GNE* mutations ($p = 0.038$) *(Table 5)*.

When comparing soleus muscle involvement across *MATR3*, *ADSSL1*, or *TTN* mutations, statistics showed no difference between these mutations in terms of mean muscle involvement ($p = 0.54$). Similarly, no statistically significant differences were found in the mean involvement of the vastus intermedius or vastus lateralis between *MYH7*, *TTN*, and *ADSSL1* ($p > 0.05$) *(Table 5).*

Muscle	MYH7	TTN	GNE	MATR3	ADSSL1	DYSF
Deltoid	<10%	<10%	<10%			<10%
Infraspinatus						<10%
Supraspinatus						<10%
Ant serratus						
Trapezius	<10%	<10%	<10%			
Triceps	<10%	<10%	<10%			<10%
Brachialis						<10%
Biceps brachii	<10%					<10%
Forearm anterior		30-50%	30-50%			<10%
Forearm posterior		30-50%	30-50%			

Table 2. *Diagnostic algorithm presenting the patterns of muscular involvement by different mutations (upper limbs).*

Regarding the tibialis anterior, mutations in the *GNE* gene appeared to be correlated with more severe involvement compared to *MYH7*, *MATR3*, and *TTN* mutations. Comparisons between *MYH7* & *DYSF*, *MYH7* & *GNE*, DYSF & *GNE*, and *DYSF* & *TTN* pairs showed statistically significant differences in tibialis anterior involvement *(Table 5)*. To compare muscle involvement between two muscles within each mutation group, the Wilcoxon test was performed *(Table 6)*. Comparison of tibialis anterior versus tibialis posterior involvement revealed a significantly higher involvement of tibialis anterior in *MYH7* (30.8 vs. 1.7), *TTN* (68.6 vs. 6.9), *GNE* (50.4 vs. 8.6), and *DYSF* (72.0 vs. 4.0) cases *(Table 6)*.

In the comparison between the brachialis and biceps brachii muscles (0 vs. 4.3), the mutations in the *MYH7* gene were significantly related to biceps brachii muscle involvement ($p < 0.001$). Medial gastrocnemius involvement was preferred by *GNE* mutations compared to lateral gastrocnemius (24.1 vs. 3.6, $p = 0.002$) *(Table 6).*

Furthermore, the semimembranosus was preferentially involved in *MATR3* cases compared to the semitendinosus muscle (30.5 vs. 6.5, $p = 0.044$) *(Table 6)*.

DISCUSSION

To assess the patterns of muscle involvement in MRI scans for differentiating distal myopathies, we established a literature-based template of MRI characteristics in genetic mutations known to cause distal myopathies.

A review by Bugiardini et al. calculated the overall sensitivity and specificity of the MRI pattern recognition as 50% and 32%, respectively. For some mutations (*MYOT*, *MYH7*, *GNE*, *TTN-MERF* mutations), the sensitivity ranged from 0-100%, but the specificity remained high (90-100%). This variability in sensitivity can be attributed to the rare nature of these diseases and the inevitably large confidence intervals[18].

While the tibialis anterior consistently was the most severely affected muscle in *MYH7*, *TTN*, *GNE*, and *DYSF* mutations (Mercuri score 3), the accompanying patterns were significantly different for each mutation. These differences provide us with valuable diagnostic clues.

GNE myopathies are a group of rare, autosomal recessive, and slowly progressive distal myopathies caused by mutations in the *GNE* gene, which encodes a key enzyme in the sialic acid biosynthesis pathway[14,31]. *GNE* mutations showed a distinctive pattern of severe tibialis anterior involvement followed by moderate infiltration of the medial gastrocnemius and hamstring muscles. The quadriceps and popliteus tended to be spared, as observed in other studies[14,32]. Indeed, Quadriceps sparing remains one of the most reliable imaging clues to distinguish *GNE* myopathy from other distal myopathies such as *DYSF* or *TTN*. Our results aligned with a study by Tasca et al.[33], which found that the tibialis anterior was completely infiltrated by fat or atrophic in most of the patients, with sparing of the quadriceps, peroneus, and popliteus[33]. Another study by Liu et al.[34] confirmed early involvement of the tibialis anterior and extensor digitorum longus, with quadriceps involvement only in advanced stages[34]. The discrepancies between our study and other studies could be due to the different stages of the disease among the reported cases, as different stages of myopathic diseases may cause different patterns of muscle involvement.

Comparatively, we observed that *GNE* mutations tended to affect tibialis anterior more severely than *MYH7*, *MATR3*, and *TTN* mutations, in addition to preferential involvement of the medial over lateral gastrocnemius.

Dysferlinopathy is an autosomal recessive muscular dystrophy caused by dysferlin deficiency, a membrane protein in the sarcolemma, due to mutations in the DYSF gene[35].

In our review, *DYSF* mutations dominantly affected the tibialis anterior and gastrocnemius, with a distinctive characteristic of early muscle edema before fat

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Muscle	MYH7	TTN	GNE	MATR3	ADSSL1	DYSF
G. max	<10%		<10%	<10%		<10%
G. med	<10%	20-30%	<10%	10-20%		<10%
G. min	<10%	<10%	<10%	20-30%		<10%
Semi. mem	<10%	20-30%	20-30%	30-40%	<10%	<10%
Semi. tendinosus	<10%	20-30%	20-30%	<10%	<10%	<10%
Add. mag	<10%		<10%	<10%	<10%	<10%
Add. longus	<10%		<10%	<10%	<10%	<10%
Biceps F. SH	<10%	20-30%	20-30%	10-20%	10-20%	<10%
Biceps F. LH	<10%	20-30%	10-20%	10-20%	<10%	<10%
Gastro. med	<10%		20-30%	>40%	>40%	20-30%
Gastro. lat	<10%	<10%	10-20%	>40%	>40%	20-30%
Soleus	<10%	20-30%	10-20%	30-40%	>40%	<10%
Iliopsoas	<10%		10-20%	20-30%		<10%
T. fascia latae	<10%			<10%	<10%	<10%
Gracilis	<10%		<10%		10-20%	
Sartorius	<10%		<10%	<10%	10-20%	
V. medialis	10-20%	<10%		<10%	>40%	<10%
V. intermedius	10-20%			<10%	>40%	<10%
V. lateralis	10-20%	<10%		<10%	>40%	
Tibialis ant.	30-40%	>40%	>40%	20-30%	10-20%	30-40%
Ext. digitorum	10-20%	30-40%	<10%	10-20%	10-20%	<10%
Peroneus	<10%	20-30%	<10%	<10%	<10%	<10%
Tibialis post.	<10%	<10%	<10%	10-20%	10-20%	<10%
Popliteus	<10%			10-20%	10-20%	

Table 3. *Diagnostic algorithm presenting the patterns of muscular involvement by different mutations (lower limbs).*
Abbraviations: Add, adductor; f, femoris; G, gluteus; Gastro, gastrocnemius; Lat, lateral; LH, Long head; Max, maximus; Mag, magnus; Min, minimus; Med, medial; Semimem, semimembranosus; SH, short head; T, tensor; V, vastus; Ant, anterior; Ext, extensor; Post, posterior.

infiltration[36]. Another finding was the high frequency of muscle edema in MRI sequences[37]. Fanin et al.[38] described STIR hyperintensities (in favor of edema) in the tibialis anterior, gastrocnemius, adductor magnus, and hamstrings, followed by progressive fat infiltration[38]. In a study by Bardakov et al.[36] edema was found most frequently in the vastus muscles, as well as in the gluteus maximus and medius. These findings suggest that in dysferlinopathy edema represents early disease stages.

Our review found that among *DYSF* mutations, the gracilis, sartorius, and vastus lateralis were spared, as consistent with prior studies[37]. The discrepancies between our study with some studies noting hamstring dominance[37], others emphasizing anterior thigh edema[36] are likely due to the type of muscle involvement. Muscle involvement in dysferlinopathy patients can present as edema or fat replacement. Most studies did not distinguish between these conditions when reporting imaging findings.

Slow-β myosin heavy chain is a protein encoded by the *MYH7* gene, expressed both in cardiac ventricular muscle and type 1 striated muscle fibers[39,40]. The vastus muscles and extensor digitorum longus were less involved than the tibialis anterior. Our results were consistent with a review conducted by Dabaj et al.[41], which also reported frequent involvement of the adductor longus with partial sparing at the edges. Additionally, the triceps and wrist extensors were commonly affected in the upper extremities[41].

The *TTN* gene encodes a scaffold protein responsible

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Muscles	MYH7	TTN	GNE	MATR3	ADSSL1	DYSF	IRA (k)
Deltoid	1	1	1	0	0	1	0.94
Infraspinatus	0	0	0	0	0	1	0.91
Supraspinatus	0	0	0	0	0	1	0.86
Ant serratus	0	0	0	0	0	0	0.84
Trapezius	1	1	1	0	0	0	0.88
Triceps	1	1	1	0	0	1	0.89
Brachialis	0	0	0	0	0	1	0.86
Biceps brachii	1	0	0	0	0	1	0.89
Forearm ant.	0	1	1	0	0	1	1.00
Forearm post.	0	1	1	0	0	0	0.89
G. max	1	0	1	1	0	1	0.93
G. med	1	1	1	1	0	1	0.91
G. min	1	1	1	2	0	1	0.90
Semi.mem	1	1	2	3	1	1	0.91
Semi. tendinosus	1	1	2	1	1	1	0.90
Add. mag	1	0	1	1	1	1	0.88
Add. longus	1	0	1	1	1	1	0.86
Biceps F. short	1	1	2	1	1	1	0.87
Biceps F. long	1	1	1	1	1	1	0.89
Gastroc. med	1	0	2	3	3	2	0.91
Gastroc. lat	1	1	1	3	3	1	0.87
Soleus	1	1	1	2	3	1	0.92
Iliopsoas	1	0	1	2	0	1	0.90
Quad. femoris	1	0	1	1	1	1	0.93
T. fascia latae	1	0	0	1	1	1	0.89
Gracilis	1	0	1	0	1	0	0.88
Sartorius	1	0	1	1	1	0	0.90
V. medialis	1	1	0	1	3	1	0.92
V. intermedias	1	0	0	1	3	1	0.91
V. lateralis	1	1	0	1	3	0	0.90
Tibialis ant.	3	3	3	2	1	3	0.94
Ext. digitorum	1	2	1	1	1	1	0.89
Peroneus	1	1	1	1	1	1	0.87
Tibialis post.	1	1	1	1	1	1	0.88
Popliteus	1	0	1	1	1	1	0.93

Table 4. *Mean fatty infiltration of the muscles evaluated on the Mercuri scale.*
Abbreviations; IRA(k), inter-rater agreement analysis using Fleiss' kappa; Add, adductor; ant, anterior; Ext, extensor; f, femoris; G, gluteus; Gastro, gastrocnemius; Lat, lateral; LH, long head; Max, maximus; Mag, magnus; Min, minimus; Med, medial; Semimem, semimembranosus; S, semi; SH, short head; T, tensor; V, vastus; Post, posterior; Quad, quadriceps.

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Muscle	Mutation	Mean of % of muscle involvement †	p value
Semi membranous	TTN	27± 16	**0.019**
	MART3	38± 30	
Biceps femoris short	GNE	20± 14	**0.038**
	TTN	23± 16	
Soleus	MART3	32± 26	0.540
	ADSSL1	58± 49	
	TTN	26± 21	
Vastus intermedius	MYH7	12± 11	0.136
	TTN	20± 18	
	ADSSL1	51± 39	
V. Lateral	MYH7	10± 11	0.122
	TTN	21± 17	
	ADSSL1	53± 42	
Tibialis Anterior	GNE	49± 35	**0.000 ¥**
	DYSF	32± 30	
	MYH7	30± 31	
	TTN	68± 36	

Table 5. *Comparison of muscle involvement between myopathies based on muscle fat infiltration (%).*

Each row represents one muscle involved in one myopathy of interest

† Each cell shows the mean ± standard deviation. A mean <10 is not reported due to difficulty in use in practice.

‡ Statistical test: Mann-Whitney test was performed for the selected muscle between the considered myopathy

All other myopathies are present in this table. Bold values represent the significant results.

¥ Comparing MYH7 & DYSF, MYH7 & GNE, DYSF & GNE, DYSF & TTN pairs showed statistically significant differences.

	MYH7	TTN	GNE	MATR3	ADSSL1	DYSF
Brachialis vs biceps brachi	0.0 vs 4.3 (p = 0.000)	---	---	---	---	---
Tibialis ant vs tibialis post	30.8 vs 1.7 (p = 0.000)	68.6 vs 6.9 (p = 0.000)	50.4 vs 8.6 (p = 0.001)	---	---	72.0 vs 4.0 (p = 0.018)
Biceps Femoris SH vs LH	---	---	---	---	---	---
Gastroc med vs lat	---	---	24.1 vs 3.6 (p = 0.002)	---	---	---
Semi-mem vs semi-tend	---	---	---	30.5 vs 6.5 (p = 0.044)	---	---

Table 6. *Comparison of muscle involvement between two muscles or groups of muscles for each mutation.*

Each column represents one mutation. Each row represents the compared muscles. Each cell shows: the mean of the muscle involvement for the first muscle studied versus the second muscle (p value).

The Wilcoxon test was performed for this comparison. Significant results are reported.

Abbreviations: Gastroc, gastrocnemius; ant, anterior; lat, lateral; LH, long head; med, medial; semi-mem: semimembranosus; semi-tend, semitendinosus; SH, short head; post, posterior.

for myofibrillar assembly. Mutations in this gene have been correlated with various skeletal muscle diseases, cardiomyopathies, and combinations thereof[42,43]. Our study showed that among TTN cases, the anterolateral compartment of the leg had the highest score of fatty infiltration. This was followed by the posterior thigh muscles. These results were consistent with previous studies that described the semitendinosus, along with the gluteus medius and other hamstring muscles, were predominantly affected in TTN, with sparing of the adductors, gracilis, and sartorius[44,45]. The sparing of the adductors, gracilis, and sartorius serves as a distinguishing hallmark of *TTN*-

related myopathies.

MATR3 was first identified as a part of the nuclear matrix which have multiple functions, including DNA binding and transcriptional regulation[46,47]. In our review, the posterior leg compartment was predominantly affected in *MATR3*-associated myopathies. Moderately involved muscles included the gluteus medius and intermedius, the iliopsoas, the semimembranosus, the biceps femoris, and the distal leg muscles. Our results were comparable to those of Mensch et al.[15].

ADSSL1 is a muscle-specific enzyme responsible for converting inosine monophosphate to adenosine monophosphate[48]. Among *ADSSL1*-related myopathies, our observations were in accordance with previous studies that showed severe involvement of the anterior thigh and the posterior leg compartments as the disease progresses[49,50].

While *MYH7* and *TTN* mutations both affected the tibialis anterior, their overall patterns were different. *TTN* mutations showed moderate involvement of the extensor digitorum and gluteus medius, with sparing of adductors and sartorius. MATR3 mutations preferentially involved the posterior leg compartment, particularly the gastrocnemius and semimembranosus, and sparing of the gracilis. *ADSSL1* mutations were unique in their severe involvement of both vastus and posterior leg muscles.

In this review article, we presented muscle MRI patterns across various genetic distal myopathies. By highlighting the characteristic imaging features of common mutations, we aim to guide readers in understanding the common MRI patterns of common myopathies and facilitate easier comparison for more accurate diagnosis.

Distal myopathy is classified as progressive atrophy and weakness of distal muscles. Later on, as the disease progresses, other muscle groups, such as proximal, cardiac, and respiratory muscles, may be involved. Therefore, the muscle involvement, the clinical presentation and imaging findings can vary based on the disease stage[51,52]. However, most of the reviewed studies did not break down the results by severity of the disease and did not mention the disease staging. This lack of information limited our ability to evaluate specific patterns of muscle involvement in each stage. Future studies should address this limitation for a more detailed analysis.

Even so, most of the studies reviewed didn't break down results by severity or mention how far the illness had advanced. Because of this gap, it was tough to spot how muscle issues change at different stages. Going forward, work should focus on tracking disease phase more closely, so we can see how muscle problems evolve over time.

In studies presenting images, we used three trained persons to estimate the muscle severity of involvement for more accuracy, and reported inter-rater agreement. To have practical and clear results and not be crowded in this systematic review, we used data from just six mutations for classifications and interpretations. Another limitation is the small number of patients in some mutations we used for analysis. However, to our knowledge, this is one of the limited systematic reviews to pool MRI findings of congenital distal myopathies for accurate diagnosis.

CONCLUSION

We described the pattern and severity of muscle involvement at the level of the upper and lower limbs in patients with hereditary distal myopathies according to MRI scans. Utilizing these patterns can expedite diagnostic work-ups by narrowing down the genes to be evaluated and by helping to identify the best muscle to sample. Given the relatively rare nature of these myopathies, we recommend further evaluation in a greater number of patients, as well as assessment of each stage of disease, specifically to correctly address the pattern.

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