Panorama of the distal myopathies

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Distal myopathies are genetic primary muscle disorders with a prominent weakness at onset in hands and/or feet. The age of onset (from early childhood to adulthood), the distribution of muscle weakness (upper versus lower limbs) and the histological findings (ranging from nonspecific myopathic changes to myofibrillar disarrays and rimmed vacuoles) are extremely variable. However, despite being characterized by a wide clinical and genetic heterogeneity, the distal myopathies are a category of muscular dystrophies: genetic diseases with progressive loss of muscle fibers. Myopathic congenital arthrogryposis is also a form of distal myopathy usually caused by focal amyoplasia.

Massive parallel sequencing has further expanded the long list of genes associated with a distal myopathy, and contributed identifying as distal myopathy-causative rare variants in genes more often related with other skeletal or cardiac muscle diseases.

Currently, almost 20 genes (*ACTN2, CAV3, CRYAB, DNAJB6, DNM2, FLNC, HNRNPA1, HSPB8, KHLH9, LDB3, MATR3, MB, MYOT, PLIN4, TIA1, VCP, NOTCH2NLC, LRP12, GIPS1*) have been associated with an autosomal dominant form of distal myopathy. Pathogenic changes in four genes (*ADSSL, ANO5, DYSF, GNE*) cause an autosomal recessive form; and disease-causing variants in five genes (*DES, MYH7, NEB, RYR1* and *TTN*) result either in a dominant or in a recessive distal myopathy. Finally, a digenic mechanism, underlying a Welander-like form of distal myopathy, has been recently elucidated. Rare pathogenic mutations in *SQSTM1*, previously identified with a bone disease (Paget disease), unexpectedly cause a distal myopathy when combined with a common polymorphism in *TIA1*.

The present review aims at describing the genetic basis of distal myopathy and at summarizing the clinical features of the different forms described so far.

Key words: distal myopathy, rimmed vacuoles, myofibrillar myopathy

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Introduction

The term distal myopathy refers to a long list of genetic muscle diseases presenting at the onset with weakness of distal extremities, usually combined with progressive atrophy of the corresponding distal muscles. Other muscles, including proximal muscles and/or cardiac and respiratory muscles, can be affected at a later stage of the disease. The clinical phenotype is extremely variable, ranging from severe forms with earlier onset and loss of ambulation to very mild late adult onset forms. Other muscle

diseases (genetically determined or acquired) may present with a distal phenotype, making the diagnostic process more complex.

Although two patients with weakness in hands and in legs or feet were first described as distal myopathy by Gowers over 100 years ago [1], only in 1998 the first genetic defect underlying a distal myopathy was identified [2]. Ten years ago, in 2010, only fourteen causative genes were known. In the last years, massive parallel sequencing has contributed to identify disease-causing variants in novel genes and to elucidate the first example of a digenic mechanism causing a distal myopathy (Tab. I). At the same time, the number of causative variants, identified in large resequencing projects, has exponentially increased [3-7]. Interestingly, most currently known genes are also responsible for separate different clinical entities, confirming the extreme phenotypic divergence observed in the field of genetic myopathies [8].

More advanced histopathological techniques and refined cell and molecular biology studies have resulted in a better understanding of the pathophysiology of distal myopathies. Clinical, histopathological, and imaging features of each form have been partly clarified, addressing the diagnosis, and supporting a proper interpretation in case of novel variants identified in previously known genes.

Adult – late onset distal myopathies

Welander distal myopathy (WDM) – TIA1

WDM was first described in several Swedish families in 1951 as an autosomal dominant late adult-onset (usually over 50 years) disease with a prominent early involvement of fingers and wrist extensors [9]. As the disease progresses, weakness involves also finger flexors, toe and ankle extensors. The disease course is usually slowly progressive, and patients remain ambulant. Histopathology features include rimmed vacuoles.

A missense variant (p.E384K) in *TIA1* gene causing the disease was identified in 2013 [10]. *TIA1* encodes an RNA-binding protein involved in the alternative splicing of specific pre-mRNAs [11-14], and is a key molecule in stress granules, regulators of RNA-translation metabolism that show altered dynamics in WDM [10].

Digenic SQSTM1 and TIA1 mediated distal myopathy

Patients with a Welander distal myopathy phenotype but negative for causative rare mutations in *TIA1* were discovered to have instead a common polymorphism in the *TIA1*, which, with a population frequency of 1%, could not be the cause of the disease. Further gene pan-

el sequencing in these patients showed the presence of *SQSTM1* mutations previously known to cause the Paget's disease of the bone, a dominant disease with reduced penetrance [15]. Functional studies showed that the *SQSTM1* gene product, p62, interferes with the same stress granule dynamics pathway as *TIA1* explaining the background for the digenic mechanism [15]. This genetic combination of rare *SQSTM1* causative variants and the common *TIA1* polymorphism did not result in a Paget disease of the bone but caused the canonical Welander phenotype. On the other hand, a cohort of 50 patients with Paget disease of the bone carrying the same *SQSTM1* mutations did not have the *TIA1* polymorphism [15].

Tibial muscular dystrophy (Udd myopathy) – the first human titinopathy

Tibial muscular dystrophy (TMD) or Udd myopathy was described in 1993 in Finnish patients [16]. Weakness in ankle dorsiflexion and atrophy of anterior lower leg muscles (often asymmetric) start after age of 35 or much later. Progression is slow and walking is usually preserved. Extensor digitorum brevis and hand muscles are normally spared. Serum CK is normal or mildly elevated and muscle imaging shows fatty degeneration in anterior tibial muscles and at later stage in all long toe extensors, hamstring and medial gastrocnemius muscles.

Muscle biopsy shows myopathic changes with acid phosphatase, ubiquitin, p62 and LC3 positive in the affected muscles, but in preserved muscles there is only a slight increase of internal nuclei.

In Finnish TMD patients, a common founder mutation (FINmaj) in the last exon of titin gene (*TTN*) was identified in 2002 [17]. FINmaj is a complex 11-bp insertion–deletion resulting in substitution of four amino acids without any frameshift and preserving the downstream amino acid sequence. Following the FINmaj identification, missense variants in the same exon (364) were also identified in non-Finnish patients [17-19].

TTN gene encodes titin, the third filament system of the sarcomere [20]. Titin interacts with several important proteins, including calpain-3 that binds the C-terminal portion of titin [21,22]. Through a large number of alternative splicing events, *TTN* encodes for a large number of different transcripts, developmental-stage or tissue specific [23,24]. Reflecting the size and complexity of titin, causative variants result in allelic diseases affecting skeletal muscle, heart or both of them, referred to as 'titinopathies' [25,26]. Dominant titinopathies include the aforementioned TMD, and the hereditary myopathy with early respiratory failure (HMERF) caused by missense variants in exon 344 [17,27-29]. Recessive titinopathies include a wide spectrum of diseases with a prenatal, congenital, childhood or later onset [30,31]. A recessive form of early/juvenile onset recessive distal titinopathy is further

Table I. List of distal myopathies and causative genes.

Clinical entity	Gene(s)	Trasmission	References
Adult – late onset distal myopathies			
Welander distal myopathy	*TIA1*	AD	Hackman et al., 2012
Digenic SQSTM1 and TIA1 mediated distal myopathy	*SQSTM1+TIA1*	DG	Lee et al., 2018
Tibial muscular dystrophy (Udd myopathy)	*TTN*	AD	Hackman et al., 2002
Vocal cord and pharyngeal distal myopathy	*MATR3*	AD	Senderek et al., 2009
Distal Actininopathy	*ACTN2*	AD	Savarese et al., 2019
Distal Myopathy with sarcoplasmic bodies	*MB*	AD	Olive et al., 2019
Oculopharyngeal distal myopathy	*NOTCH2NLC, LRP12 and GIPC1*	AD	Deng et al., 2020; Ishiura et al., 2019; Saito et al., 2020; Sone et al., 2019
PLIN4 mutated distal myopathy	*PLIN4*	AD	Ruggieri et al. 2020
VCP distal myopathy	*VCP*	AD	Palmio et al 2011
Myofibrillar distal myopathies			
Distal myopathy with myotilin defect	*MYOT*	AD	Penisson-Besnier et al., 2006
Late onset distal myopathy (Markesbery-Griggs, Zaspopathy)	*LDB3*	AD	Griggs et al., 2007
Desminopathy	*DES*	AD > AR	Sjoberg et al., 1999
Alpha-B crystallin-mutated distal myopathy	*CRYAB*	AD	Reichlich et al. 2010
Early adult onset distal myopathies			
Miyoshi myopathy	*DYSF*	AR	Liu et al., 1998
Recessive distal titinopathy	*TTN*	AR	Evila et al., 2017
Distal myopathy with rimmed vacuoles (Nonaka and GNE myopathy)	*GNE*	AR	Kayashima et al., 2002
Distal ABD-filaminopathy	*FLNC*	AD	Duff et al., 2011
DNAJB6 distal myopathy	*DNAJB6*	AD	Ruggieri et al., 2015 - Palmio et al., 2020
Rimmed vacuolar neuromyopathy	*HSPB8*	AD	Ghaoui et al., 2016
ANO5 distal muscular dystrophy	*ANO5*	AR	Bolduc et al., 2010
RYR1 mutated calf predominant distal myopathy	*RYR1*	AD/AR	Laughlin et al., 2017 - Jokela et al., 2019
Early-childhood onset distal myopathies			
Early onset distal myopathy (Laing)	*MYH7*	AD > AR	Meredith et al., 2004
Early onset distal myopathies with nebulin defect	*NEB*	AR > AD	Wallgren-Pettersson et al., 2007, Kiiski et al., 2019
Early onset ADSSL distal myopathy	*ADSSL*	AR	Park et al., 2016
Early onset distal myopathy with KLHL9 mutations	*KLHL9*	AD	Cirak et al., 2010
Other myopathies and dystrophies with distal weakness			
Distal myopathy with caveolin defect	*CAV3*	AD	Tateyama et al., 2002
DNM2 related distal myopathy	*DNM2*	AD	Bitoun et al., 2005

AD: autosomal dominant; AR: autosome recessive; DG: digenic

discussed below in this review. With the increasing number of reported patients, first insights on the genotype-phenotype correlation are achieved [30]. *TTN* variants are also associated with dilated and hypertrophic cardiomyopathy [32,33].

Vocal cord and pharyngeal distal myopathy – MATR3

First described in a large North American family [34] and later in a large Bulgarian pedigree [35], vocal cord and pharyngeal distal myopathy (VCPDM) is characterized by adult-onset (between 35 and 60 years) distal weakness and weakness of vocal cord and pharyngeal muscles. Limb weakness can be asymmetric and the phenotype is highly variable in terms of age of onset, progression and muscle weakness distribution [34,36,37]. Most patients develop respiratory failure [38]. CK levels are normal or mildly

elevated. EMG shows myopathic changes and rimmed vacuoles are present in the biopsy. Muscle MRI shows a predominant involvement of the lower legs both anterior and posterior compartment and hamstrings in thighs [39].

The underlying re-occurring p.S85C mutation was identified in *MATR3* gene [35]. *MATR3* encodes matrin-3, a protein located in the nuclear matrix where it regulates several processes related to gene expression, RNA splicing and export of RNA and nuclear proteins [40,41]. Variants in *MATR3* have also been identified in patients with amyotrophic lateral sclerosis (ALS) [42].

Distal Actininopathy – ACTN2

Distal actininopathy is an autosomal dominant, adult onset distal myopathy starting usually with foot drop. The disease later progresses to proximal lower limb muscles while upper limbs remain relatively spared [43]. Serum CK levels are mildly elevated and muscle biopsy shows rimmed vacuoles with some myofibrillar disarrays and undulation of the Z-disk on electron microscopy [43].

The underlying genetic defects in the four families reported so far are heterozygous missense variants in the *ACTN2* gene. *ACTN2* encodes alpha-actinin2, a structural molecule of the Z-disks that interacts with titin and acts a scaffold of many other Z-disk located proteins such as myotilin [44-47].

Variants in *ACTN2* also cause congenital myopathy with structured cores and Z-line abnormalities [48]. Moreover, dilated cardiomyopathy and hypertrophic cardiomyopathy have been associated with missense variants in *ACTN2* [49-53].

Distal Myopathy with sarcoplasmic bodies – MB

In 1980 Edström et al. published a Swedish family with this title [54]. Only recently, the genetic cause of the disease was identified with one unique causative variant in Myoglobin (*MB*), reoccurring in several unrelated families [55]. In these later studied families, the characteristic muscle pathology was evident but the clinical phenotype was more proximo-distal and not particularly distal [55].

Oculopharyngeal distal myopathy OPDM – CGG and GGC expansions

The peculiar combination of severe adult onset distal atrophies in limb muscles and facial weakness, ptosis and dysphagia can occur both in dominant and recessive families and in sporadic patients [56,57]. In the studied patients, the muscle pathology is a rimmed vacuolar myopathy. In the two last years the cause of many Asian dominant families have been clarified as caused by triplet repeat expansions, both CGG and GGC, in three different genes *NOTCH2NLC*, *LRP12* and *GIPC1* [58-61]. The repeats are

translated into aggregating protein products and the host gene functions are not supposed to contribute to the disease mechanism.

PLIN4 mutated distal myopathy – PLIN4

A large Italian family with an autosomal dominant adult-onset distal myopathy and histopathological features of rimmed vacuoles was first described in 2004 [62]. Linkage analysis suggested that the causative gene could have been localized in the 19p13.3 locus [62].

Recently, Ruggieri et al. identified the underlying genetic defect in the *PLIN4* gene, encoding for perilipin-4 [63]. Thirty-one repeats of 99 nucleotides in exon 4 of *PLIN4* encode the 31x33 amino acid amphipathic domain of perilipin-4. An expansion of the normal repeat to 40×99 bases, resulting in 297 (9×33) extra amino acids, has been identified in the affected members of the family.

Perilipin-4 is a member of the perilipin family, a group of proteins that coat the surface of lipid droplets [64]. Perilipin-4 is highly expressed in skeletal muscle with a possible role in lipid metabolism. The identified repeat expansion in patients with *PLIN4*-related distal myopathy seems to cause a misfolding and leads to protein accumulation in vacuoles disrupting the myofibrillar organization [63].

VCP distal myopathy – VCP

Initially described by Palmio and colleagues in a large dominant Finnish family, *VCP*-related distal myopathy has an onset in mid-adulthood mainly affecting anterior leg muscles [65]. After 25 years of disease, the patients became affected by a progressive frontotemporal dementia. None of the patients had signs of Paget disease of the bone. Serum CK levels are normal or slightly elevated. Myopathic changes with rimmed vacuoles are observed in the muscle biopsy. MRI shows degenerative changes of anterior lower leg muscles.

Although a clinical variability has been observed [66-73], the most common phenotype of pathogenic *VCP* variants is proximal myopathy with scapular winging, Paget disease and frontotemporal dementia (IBMPFD) [74-76].

Myofibrillar distal myopathies

Distal myopathy with myotilin defect – MYOT

A late-onset distal myopathy has been associated with heterozygous variants in *MYOT* gene [77-79]. The first symptoms, weakness of ankle dorsiflexion and/or calf muscles, occur after age 50 years but, despite late onset, the further progression can be rapid. Respiratory and cardiac muscles are spared.

Histopathological features are consistent with myofibrillar myopathy and include rimmed and non-rimmed vacuoles, and myofibrillar disorganization with myotilin accumulations [79-81]. Muscle imaging shows that soleus is typically the first muscle affected followed by tibialis anterior and gastrocnemius medialis muscles [82,83].

The most common causative variants in *MYOT* are missense changes affecting serine and threonine amino acids in the serine rich domain. *MYOT* gene encodes myotilin, a key component of the Z-disc, directly binding F-actin [84]. Some patients have been described as affected by a dominant limb-girdle muscular dystrophy (previously LGMD1A) [85,86], but distal myopathy is the main phenotype. A proximal muscle involvement is only observed in later stages or in homozygosity for known dominant variants [87,88]. The term 'spheroid body myopathy' was also used since the protein aggregates in some cases have the corresponding shape [89,90].

Late onset distal myopathy (Markesbery-Griggs, Zaspopathy) – LDB3

The dominant *LDB3*-related distal myopathy usually starts with ankle weakness after the age of 40 years with later involvement of proximal muscles [91-94]. Cardiomyopathy can occur very late; facial and respiratory muscles are preserved. Muscle biopsy reveals myofibrillar myopathy with rimmed and non-rimmed vacuoles [95]. Myofibrillar protein accumulations are similar with myotilinopathy and desminopathy [96].

LDB3 encodes the lim domain-binding 3 protein, also called Z-band alternatively spliced PDZ motif-containing protein (ZASP) that interacts with other Z-disk proteins [97,98]. Hypertrophic and dilated cardiomyopathies (with or without left ventricular noncompaction) are allelic disorders [99,100].

Desminopathy – DES

Desmin-related distal myopathy is a myofibrillar myopathy with cytoplasmic accumulation of desmin in cardiac and skeletal muscles. The first family was described in 1943 long before the gene was known [101,102]. Cardiomyopathy and cardiac conduction defects are frequent, and the weakness/atrophy involves both hands and lower legs with later spread to proximal muscles. MRI shows the early involvement of peroneal muscles followed by tibialis anterior, gastrocnemius and soleus muscles [80,82]. CK is usually slightly elevated.

The fist causative variants in DES were identified in 1998 [103]. DES encodes desmin, a protein of the intermediate filament connecting Z-band with the plasmalemma and the nucleus[104]. As suggested by a recent study, desmin forms seeding-competent amyloid that is toxic to myofi-

bers and disease-causing mutations enhance the amyloid formation [105]. Most patients have a dominant disease with onset in early adulthood but a later onset is possible [106]. Rare cases with a recessive, more severe, form have been reported [107]. Dominant cardiomyopathy without skeletal muscle disease, scapuloperoneal and other phenotypes, due to the increasing number of causative variants identified, are also reported [108-112].

Alpha-B crystallin-mutated distal myopathy – CRYAB

In 1998, Vicart and colleagues identified the first causative variant in the *CRYAB* gene causing a myopathy with accumulation of aggregates of desmin [113]. In 2003, Selcen et al described patients with a generalized proximal and distal myopathy affecting also the cardiac and respiratory function and carrying mutations in *CRYAB* [114]D. In 2010 and in 2012, two studies identified patients with *CRYAB* mutations and a distal adult-onset myofibrillar myopathy [115,116]. *CRYAB*-related distal myopathy mainly involves the anterior part of the distal leg at the early stage and progresses with a milder proximal weakness. Cataracts are the hallmark and dysphagia, dysphonia, respiratory failure, and cardiomyopathy may be associated. Muscle MRI shows fatty degenerative changes in tibialis anterior, gastrocnemius medialis muscles and vastus muscles [82,115,117,118].

CRYAB encodes alpha-B-crystallin, also called HSPB5, a member of the small heat-shock protein family, a molecular chaperone that interacts with desmin in the assembly of intermediate filaments [119-122].

Causative *CRYAB* variants also cause a dominant dilated cardiomyopathy, congenital cataract (dominant and recessive) and a more severe, usually recessive myopathy (fatal infantile hypertonic myofibrillar myopathy) [123-127].

Early adult onset distal myopathies

Miyoshi myopathy – DYSF

Miyoshi and colleagues first described patients in the sixties with early adult-onset weakness, myalgia and atrophy in calf muscles [128]. Serum creatine kinase (CK) is highly elevated already in the early stages of the disease or even in presymptomatic patients. Muscle imaging shows marked involvement of posterior lower legs. Muscle biopsy shows myopathic changes with necrotic fibers in the calf muscles and inflammation is a common finding.

Dysferlin (*DYSF*) as causative gene with biallelic recessive mutations was identified in 1998 [2]. Dysferlin is a ubiquitous transmembrane protein with a high skeletal muscle expression. The protein most probably acts

in calcium-mediated sarcolemmal fusion events and re-sealing [129-131]. Dysferlin expression by immunostaining or western blot (even from blood leucocytes) is useful in the diagnostic process, although the protein can be also secondarily reduced [132,133].

Myoshi myopathy and LGMDR2 Dysferlin-related (previously LGMD2B), one of the most common LGMD form in several countries [4,134,135], are allelic diseases with overlapping symptoms and signs [136,137]. LGMD patients have a more proximal involvement at the onset but, after 20 years of disease progression, the two phenotypes usually merge as dysferlinopathies [138-140].

Recessive distal titinopathy – TTN

Some nonsense, small indels causing a frameshift or splice site variants in the last and second last exons of *TTN,* initially also thought to cause dominant TMD because of dominant-looking pedigrees, later proved to be recessive [141-145]. The presence of second causative variants *in trans* explains the novel entity of early/juvenile onset recessive distal titinopathy, a more severe condition than the late onset TMD [141-143]. In some families, multiple second causative variants segregating with the disease would mimic the presence of a dominant inheritance, making the diagnosis even more complex [141,142,146].

The complexity of *TTN* gene may result in elusive variants not identified on DNA by the traditional pipelines [147]. Second tier tests, such as copy number variant (CNV) analysis and RNA sequencing, contribute to identify unrecognized pathogenic variants [148-152].

Distal myopathy with rimmed vacuoles (Nonaka or GNE myopathy) – GNE

Independently described by Nonaka et al. and by Argov and Yarom, the *GNE* distal myopathy is a rimmed vacuolar recessive myopathy with an early adult onset [153,154]. It first affects the anterior compartment of lower legs and thigh hamstring muscles with sparing of the quadriceps, but the progression is rather severe, and half of the patients loose ambulation within 10 years. Serum creatine kinase is mildly elevated and muscle histopathology is characterized by rimmed vacuoles.

The causative gene (*GNE*) was identified in 2001 [155] and, since then, patients have been reported worldwide. *GNE* encodes an epimerase-kinase enzyme involved in the sialic acid biosynthesis. Glycoproteins and glycolipids located in the membrane often undergo a sialic acid modification that seems to be crucial for their function [156]. Nevertheless, in a recent study, no consistent major change in sialylation has been observed comparing patients and matched control samples, suggesting that the pathophysiology of the disease is still unclear [157].

More than 180 variants are currently known and founder mutations first reported from Middle East and Japan have been described in many populations [158-163]. *GNE* is susceptible to Alu-mediated recombination, and copy number variants (CNV) have been reported suggesting the utility of second-tier tests in case of an uninformative sequencing analysis aiming at the identification of single nucleotide variants [164-167]. Moreover, a vast clinical heterogeneity, only partly explained by the *GNE* genotype, is observed in families with *GNE* mutations [160,168-170].

Sialuria is an allelic dominant metabolic disease characterized by the accumulation of N-acetylneuraminic acid (NeuAc) due to missense variants in GNE [171].

Distal ABD-filaminopathy – FLNC

A large Australian family with a dominant, adult-onset, slowly progressive distal myopathy was described in 2005 by Williams and colleagues [172]. In a second Italian family with otherwise similar phenotype reported by Duff et al. cardiac involvement was also present [173]. Weakness of handgrip is the usual presentation followed by calf muscle plantar flexion weakness. The progression is slow, and patients remain ambulant. CK is normal or mildly elevated, and muscle MRI shows fatty replacement in posterior compartment of lower legs. Histopathology is unspecific myopathic without vacuoles or myofibrillar abnormalities.

Combining linkage data and resequencing of candidate genes in these two families, two different missense changes in the N-terminal actin-binding domain (ADB) of *FLNC* were identified [173]. The *FLNC* gene encodes filamin, an actin ligand that plays an important role in mechanical stabilization, mechanosensation and intracellular signalling through a large network of interactors [174,175]. Mutations in other parts of the gene may cause late onset myofibrillar myopathy with generalized weakness and cardiomyopathy [176-178]. After the gene identification in 2011, novel *FLNC* causative variants have been identified, expanding the spectrum of *FLNC*-related myopathies [179-181].

Recent findings suggest a more complex genotype-phenotype correlation. A missense variant, p.M222V, in the N-terminal actin-binding domain, causing a distal myofibrillar myopathy, has been reported [182]. Another missense change, p.C203Y, has been recently found to cause an upper limb distal myopathy with nemaline bodies [183].

DNAJB6 distal myopathy – DNAJB6

The disease was originally reported by Servidei and colleagues in a large Italian family with onset of ankle weakness between the second and sixth decades of life [184], and usually progressing to proximal muscles and upper

limbs. Muscle biopsy showed dystrophic changes and rimmed vacuoles. In the Italian family, the causative variant was found in *DNAJB6*, in a different locus from the one initially reported [185]. *DNAJB6* encodes a ubiquitously expressed member of the DNAJ/HSP40 family of co-chaperones [119,186]. Mutations in *DNAJB6*, specifically in the G/F domain, cause more often a proximal myopathy (LGMD1D) [187-193]. Recently, a form of DNAJB6-related distal calf-predominant myopathy has been reported in patients with particular mutations in the N-terminal J-domain [194].

Rimmed vacuolar neuromyopathy – HSPB8

Ghaoui and colleagues reported two families with a dominant *HSPB8*-related disease showing early adult neurogenic leg weakness and progressing towards a distal and proximal myofibrillar and rimmed vacuolar myopathy in the later stage of the disease [195]. EMG revealed denervation in the distal lower limbs and myopathic proximal changes. MRI of the lower limb muscles showed first diffuse neurogenic changes in gastrocnemius, deep toe flexors, and peroneus with later fatty replacement in proximal thigh and lower legs muscles.

The *HSPB8* gene encodes the small heat-shock protein-beta 8, acting as stress protein with a chaperone-like activity and part of the chaperone-assisted selective autophagy (CASA) complex [119,196]. *HSPB8* missense variants had been previously associated with distal hereditary motor neuropathy 2A (dHMN2A) and Charcot-Marie-Tooth disease (CMT2L) [197-201]. The myofibrillar myopathy with aggregates and rimmed vacuoles mimics the histopathological changes seen in myopathies caused by defects in *BAG3* and *DNAJB6* [202,203].

Later other families with a combined neuromuscular disorder, encompassing dHMN and MFM have been described[204]. In one family decrease of *TARDBP* mRNA levels causing a consistent alteration of TDP-43-dependent splicing was reported [204]. Recently, a novel *HSPB8* variant has been found in a patient with limb-girdle myopathy without associated neuropathy [205].

ANO5 distal muscular dystrophy – ANO5

Distal anoctaminopathy has an age of onset in early/mid adulthood (18-40 years) [206,207]. Early manifestations include difficulties in sport activity and in walking on tiptoes but often the clinical presentation is mild, or the disease does not even result in overt clinical signs. The early stage hypertrophy of calf muscles progresses into muscle atrophy [208]. At a later stage, proximal muscle weakness and wasting is observed. Typically, the cardiac muscle is spared. CK levels are usually highly elevated (over 10 times the upper limits). Non-specific myopathic changes with scattered necrotic fibers are observed in the muscle biopsy.

The disease is due to bi-allelic causative variants in the *ANO5* gene, encoding for anoctamin-5, a putative cytoplasmic calcium-activated chloride channel, with a possible role in membrane fusion and repair [209,210]. The more common phenotype of bi-allelic variants in *ANO5* is late onset proximal (LGMDR12) [206,207,211-214]. Variants causing *ANO5*-related recessive anoctaminopathies mostly result in a reduced protein expression and missense changes likely destabilize the protein, causing its degradation [215,216]. We still lack a clear genotype-phenotype correlation explaining the high intrafamilial and interfamilial clinical variability observed, also considering that female patients often have a milder disease than males [206,212,217-221].

A dominant form of gnathodiaphyseal dysplasia is (GDD) an allelic disorder caused by *ANO5* missense variants in heterozygosity [222,223]. The pathomechanism of the *ANO5*-related GDD is still unclear. However, the protein seems to have an important role in the embryonic development and most probably in the osteoblast differentiation [223].

RYR1 mutated calf predominant distal myopathy – RYR1

A very mild dominant distal myopathy with preferential fatty degeneration of medial gastrocnemius, clearly shown by muscle MRI, has been recently reported in one Italian and two Finnish families [224]. Some patients exhibit toe walking in the childhood with spontaneous remission. In adulthood, patients complain of exercise myalgia in the calves, and show 5-10 fold elevated CK. No limitation of walking was present even in elderly patients. Muscle biopsy reveals core pathology. Three different *RYR1* mutations were identified in different parts of the gene, which encodes ryanodine receptor 1, a calcium release channel of the sarcoplasmic reticulum that, together with sarcolemmal voltage-gated calcium channels (DHPR), is responsible for the excitation-contraction coupling.

Dominant and recessive mutations in the *RYR1* gene present with a multitude of phenotypes including malignant hyperthermia (MH) susceptibility and congenital central core disease (CCD), centronuclear myopathy, multiminicore myopathy, congenital fibre type disproportion, axial myopathy, King-Denborough syndrome, atypical periodic paralysis and exertional rhabdomyolysis/myalgia [225-235]. A childhood-onset distal myopathy presenting with hand stiffness and facial weakness has been associated to bi-allelic *RYR1* variants [236].

Early-childhood onset distal myopathies

Early onset distal myopathy (Laing myopathy) – MYH7

Laing myopathy was the first distal myopathy with established genetic linkage [237]. The onset is in early child-

hood with the ankle dorsiflexor and toe extensor (hanging big toe) weakness and the disease has a slow progression. Severe forms develop scoliosis and involves proximal, neck and facial muscles. CK levels are normal or mildly elevated. The most consistent histopathology is hypotrophy of type 1 slow fibers, often combined with core/minicore lesions [238]. Muscle MRI shows the involvement of anterior compartment lower leg muscles and, eventually, of the sartorius, with relative sparing of the lateral gastrocnemius muscle and rectus femoris [239-242].

In 2004 the causative variant was identified in the *MYH7* gene encoding the beta heavy chain of myosin [243]. Since then, a large number of causative variants in the tail of the protein were reported, with a large proportion (30%) of re-occurring de novo mutations masking the dominant effect of the variants [244-248]. Causative variants in the head and neck domains at the N-terminal of the protein have been mainly associated with hypertrophic cardiomyopathy (without skeletal muscle involvement) [249-251]. Variants in the ultimate C-terminal region most often result in other skeletal myopathies (hyaline body myopathy) with or without cardiac involvement [252,253]. Rare recessive forms of *MYH7*-related myopathy have been reported [254-256].

Early onset distal myopathies with nebulin defect – NEB

Bi-allelic, mainly missense, variants in *NEB* gene may result in an early-onset distal myopathy with a predominant weakness of extensor muscles of feet and later hands [257,258]. The progression is very slow and adult patients do not have major disability.

Muscle imaging shows a selective fatty degeneration in the anterior tibial muscles, EMG is myopathic and CK is normal or mildly elevated. Scattered and grouped atrophic fibers (that can be misinterpreted as neurogenic changes) are detectable in the biopsy of affected muscle without rods on light microscopy [258,259]. Small rods associated with Z-disks may be present on electron microscopy [259].

A large in-frame deletion, dominantly inherited in a three-generation family with a distal nemaline rod/cap myopathy, was recently described [260]. The in-frame deletion results in a protein of reduced size with a dominant-negative effect [260]. Patients present with foot drop in childhood and the disease progresses with the involvement of distal upper limbs. CK can be slightly elevated, EMG is myopathic and muscle MRI shows fatty degeneration of the anterior compartment lower leg muscles. A large heterozygous de novo deletion in young patient with asymmetric distal and facial weakness has just been identified confirming the dominant effect of an abnormal protein (submitted).

The 183-exon *NEB* gene encodes nebulin, a protein of 600-900 kDa that regulates the length of actin filaments [261,262]. Causative variants in *NEB* (mainly nonsense, out-of-frame indels or copy number variants, and splicing variants) are the most common cause of congenital nemaline myopathy [263,264]. Additional allelic diseases are core rod myopathy, and fetal akinesia/lethal multiple pterygium syndrome [259,265,266].

Copy number variant (CNV) analysis and RNA sequencing are essential to identify possible elusive pathogenic *NEB* variants [148-150,267,268].

Early onset ADSSL distal myopathy – ADSSL

In 2016, Park and colleagues reported two unrelated Korean families with an autosomal recessive adolescent-onset distal myopathy with facial muscle weakness, mild CK elevation and rimmed vacuoles in the muscular biopsy [269,270]. Two different variants in the *ADSSL* gene were identified by exome sequencing. The *ADSSL* gene encodes the muscle isozyme of adenylosuccinate synthase, the enzyme catalysing the initial reaction in the conversion of inosine monophosphate (IMP) to adenosine monophosphate (AMP) [271,272]. Two following studies identified novel Korean and non-Korean (Turkish and Indian) patients, confirming the gene-disease association [273,274]. Most patients presented with a distal myopathy with onset in childhood or adolescence progressing to involve weakness of proximal muscles in early adulthood. However, one patient, homozygous for a missense variant, shows a proximal myopathy with contractures and muscle atrophy, expanding the *ADSSL*-related spectrum of phenotypes [274].

Early onset distal myopathy with KLHL9 mutations – KLHL9

Cirak and colleagues described a German family with an autosomal distal weakness caused by a heterozygous variant in the *KLHL9* gene [275]. Despite extensive later studies, this gene has not been confirmed in any other myopathy families.

Other myopathies and dystrophies with distal weakness

Distal myopathy with caveolin defect – CAV3

In 2002, Tateyama and colleagues described a form of sporadic distal myopathy caused by an heterozygous missense variant in *CAV3* gene [276]. Since then, additional patients and further causative variants have been reported [277,278]. Onset is in early adulthood, muscle atrophy and weakness are often limited to the small muscles of the hands and feet. Other features included calf hypertrophy, pes cavus, myalgias, slightly increased serum CK. EMG studies show a myopathic pattern and histological find-

ings include nonspecific myopathic changes [278,279]. *CAV3* expression can be reduced.

Variants in *CAV3* can also cause an isolated hyper-ckemia or a rippling muscle disease [280-285] and even cardiac phenotypes (hypertrophic cardiomyopathy and long QT syndrome) [286,287]. Some patients with *CAV3* related myopathy have been previously described as LGMD1C patients [288].

DNM2 related distal myopathy – DNM2

DNM2-related myopathy is an autosomal dominant slowly progressive centronuclear myopathy characterized by the presence of centrally located nuclei in a several muscle fibres [289]. The clinical onset is usually in childhood or early adulthood [290]. The distal muscle weakness is marked although facial weakness is the clinical lead to diagnosis [291-300]. More severe forms, clinically resembling myotubular myopathy, have been described [301]. MRI studies shows fatty infiltration of the calf muscles [302]. Electromyography may show a mix pattern with myopathic and neuropathic changes.

DNM2 encodes dynamin 2, a ubiquitously expressed GTPase that is involved in endocytosis and intracellular trafficking [303-306]. Dynamin 2 interacts with actin and has an active role in regulating microtubule networks and in centrosome function [307]. *DNM2* mutations can also cause an intermediate or axonal CMT disease with and without cataracts [308]. A lethal congenital syndrome associating akinesia, joint contractures, hypotonia, skeletal abnormalities, and brain and retinal haemorrhages has been observed in three consanguineous families with a missense variant (p.Phe379Val) in homozygosity [309].

Differential diagnostics

A long range of other myopathies needs to be considered in the differential diagnostics since they may show prominent distal weakness and/or atrophy:

- Facioscapulohumeral muscular dystrophy;
- Myotonic dystrophy type1;
- HMERF titinopathy (i.e. p.C31712R mutation);
- Scapuloperoneal syndromes (FHL-1, *TRIM32*,…);
- Other nemaline and rod-core myopathies (*TPM2*, *ACTA1*,…);
- Inclusion body myositis;
- Telethoninopathy;
- Glycogenoses: brancher and debrancher enzyme defects;
- Lipidosis in *PNPLA2* mutated disease;
- Mitochondrial distal myopathy (*POLG1*);
- Nephropathic cystinosis;
- Amyloid myopathy (myeloma induced).

Conclusions

Despite the huge developments in the last 20 years to uncover the genetic cause of distal myopathy, some families and patients still remain without a final diagnosis. The introduction of long read sequencing and RNA sequencing in clinical care and the constitution of large international consortia will most probably further increase the diagnostic rate [310-316].

The reason for some genetic defects to have preference for the distal limb muscles in causing loss of muscle tissue is unclear and understanding the molecular background for this preference may also harbour insight for therapeutic opportunities.

Considering the crucial advancements in the last decade, we can look forward optimistically to the upcoming decade. We will most probably identify an increasing number of digenic diseases and of genetic and non-genetic modifiers influencing the phenotype. The next challenge is to translate the genetic and molecular advancements in clinics, thereby contributing to the development of a personalized medicine aiming at providing a tailored approach to each patient with a distal myopathy [317,318].

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