Distal myopathies – New genetic entities expand diagnostic challenge

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Abstract

Distal myopathies are a group of muscle diseases which share the clinical pattern of predominant weakness in the feet and/or hands. Rapid advance in the understanding of underlying gene defects have to date separated more than 20 distinct disorders and many are yet without genetic characterisation. No definite diagnosis can be made on other grounds than identification of the final molecular genetic defect. Besides usual investigations including EMG and muscle biopsy, muscle imaging is very important in defining the precise pattern of muscle involvement. Based on the combination of age at onset, mode of inheritance, pathology and muscle imaging, the number of underlying candidate genes for a certain disease can be significantly reduced, which is of help for the molecular genetic approach.

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Keywords: Distal myopathy; Muscular dystrophy; MRI; Molecular genetics

1. Introduction

Four different distal myopathies had been clinically described before the new era of molecular genetics: autosomal dominant Welander distal myopathy (WDM) [1], recessive Miyoshi myopathy (MM) [2,3], recessive Distal myopathy with rimmed vacuoles (Nonaka, DMRV) [4], and dominant Tibial muscular dystrophy (Udd, TMD) [5]. Comprehensive descriptions of a few single families also represented different entities: early adult onset dominant distal myopathy (Milhorat and Wolff) [6], late onset dominant distal myopathy (Markesbery–Griggs) [7]. Molecular genetics has proved these all being caused by different genes (Table 1).

The advance in molecular genetics started in the 1990s with linkage in an Australian family with early-onset autosomal dominant distal myopathy (MPD1) [8]. Others soon followed: MM [9], DMRV [10], TMD [11], and WDM [12]. Subsequently the responsible genes and mutations in encoded proteins were identified: dysferlin for MM in 1998 [13], desmin in the Milhorat family 1998 [14], C-terminal mutations in M-line titin as the cause of TMD in 2002 [15], mutations in GNE for DMRV the same year [16], mutations in slow myosin MYH7 for Laing myopathy 2004 [17], and ZASP mutations responsible for Markesbery–Griggs myopathy 2007 [18].

New distal myopathies have expanded the list of separate diseases by molecular genetics to more than 20 different entities. The extensive developments prompt for an updated classification of the distal myopathies and for differential diagnostic algorithms to help the clinician identify the genetically determined forms (Figs. 2A and 2B). In addition, distal muscle weakness and atrophy is frequently the presenting symptom and sign in other disorders, characterized and classified on other ground by different terms, which need to be considered in the differential diagnostic approach (Table 2).

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2. Disease manifestations and findings useful in clinical practice

2.1. Late onset autosomal dominant distal myopathies

2.1.1. Welander distal myopathy

Weakness typically starts in index finger and wrist extensors usually in the fifth–sixth decade, followed by atrophy of thenar and intrinsic hand muscles. Finger and wrist flexors and weakness in toe and ankle extensors may develop after several years, although some patients have onset of weakness in the lower leg muscles. Some sensory involvement because patients may complain of cold fingers have been suggested but neuropathy has not been confirmed [19]. The progression is slow and patients have a normal life expectancy, while losing their fine motor hand skills. CK levels are slightly elevated. Muscle pathology is rimmed vacuolar with degenerated fibers leading to end-stage loss of muscle fibers in affected muscles. Muscle MRI is informative, with considerable involvement of posterior calf muscles besides fatty degenerative changes in the anterior compartment (Fig. 1C) [20].

2.1.1.1. Epidemiology. So far definitely diagnosed patients were identified only in Sweden and Finland.

2.1.1.2. Molecular genetics. Welander distal myopathy is linked to chromosome 2p13 [12]. The locus is close to, but outside of the dysferlin gene. So far no mutations have been reported. In Scandinavian patients, a common founder haplotype can be identified over the linked locus, which to some extent can be used for molecular genetic diagnostics.

2.1.2. Tibial muscular dystrophy (TMD, Udd myopathy)

Weakness starts with decreased ankle dorsiflexion usually typically after age 35–40, but late onset after age 60 may occur. Weakness can be asymmetric for years. Some proximal weakness in lower limbs is present in the eight decade; most patients remain ambulant. Extensor digitorum brevis and hand muscles are spared [21]. As with other dominant diseases variations are observed even within the family [22]. CK is slightly elevated. Muscle MRI shows highly selective fatty degeneration in lower leg anterior compartment muscles starting in tibialis anterior (Fig. 1A). Later, hamstring and gluteus minimus muscles are involved and focal changes may occur in soleus and medial gastrocnemius [23]. Muscle biopsy in the target muscle tibialis anterior muscle show rimmed vacuolated and rare necrotic fibers progressing over time to total end-stage pathology.

Table 1

<table>
<thead>
<tr>
<th>Gene</th>
<th>Protein</th>
<th>Ref.</th>
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<tr>
<td>TTN</td>
<td>Titin</td>
<td>Udd et al. [5]</td>
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<tr>
<td>TTID</td>
<td>Myotilin</td>
<td>Penisson-Besnier et al. [30]</td>
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<tr>
<td>LDB6</td>
<td>ZASP</td>
<td>Griggs et al. [18]</td>
</tr>
<tr>
<td>MATR3</td>
<td>Matrin3</td>
<td>Senderek et al. [35]</td>
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<tr>
<td>VCP</td>
<td>VCP</td>
<td>Palmio et al. [36]</td>
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<tr>
<td>CRYAB</td>
<td>zB-crystallin</td>
<td>Reichl et al. [38]</td>
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2. Adult onset autosomal dominant forms

3. Early onset autosomal dominant forms

4. Early onset autosomal recessive forms

5. Early adult onset autosomal recessive forms

6. Adult onset autosomal recessive form

2.1. Late adult onset autosomal dominant forms

6. Adult onset autosomal recessive form

Table 1

Genetically determined distal myopathies.

<table>
<thead>
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<td>Palmio et al. [36]</td>
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<td>nd</td>
<td>Reichl et al. [38]</td>
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<td>DES</td>
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<td>FLMC</td>
<td>Filamin-C</td>
<td>Duff et al. [42]</td>
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<td>nd</td>
<td>nd</td>
<td>Maljineh et al. [57]</td>
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<td>nd</td>
<td>nd</td>
<td>Servidei et al. [55]</td>
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<td>nd</td>
<td>nd</td>
<td>Felice et al. [56]</td>
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<tr>
<td>nd</td>
<td>nd</td>
<td>Durmus et al. [54]</td>
</tr>
<tr>
<td>MYH7</td>
<td>Beta-MyHHC</td>
<td>Laing et al. [8]</td>
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<tr>
<td>KHL9</td>
<td>KHL9</td>
<td>Cirak et al. [46]</td>
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<tr>
<td>NEB</td>
<td>Nebulin</td>
<td>Wallgren-Pettersson al. [47]</td>
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<td>DYSF</td>
<td>Dysferlin</td>
<td>Miyoshi et al. [2]</td>
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<tr>
<td>ANO5</td>
<td>Anoctamin-5</td>
<td>Bolduc et al. [52]</td>
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<tr>
<td>GNE</td>
<td>GNE</td>
<td>Nonaka et al. [4]</td>
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<td>nd</td>
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<td>Durmus et al. [54]</td>
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<td>nd</td>
<td>nd</td>
<td>Linssen et al. [59]</td>
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2.1.2.1. Epidemiology. TMD is the most common muscle disease in Finland with a prevalence of 20/100,000 and patients with Finnish ancestry found in several other countries. TMD families without Finnish background have been identified in France, Belgium, Spain, Italy and Switzerland ([24–27], and unpublished data).

2.1.2.2. Molecular genetics. Mutations causing this phenotype are located in the C-terminus of the giant sarcomeric protein titin. The Finnish founder mutation (FINmaj) is a complex 11 bp insertion–deletion mutation exchanging four amino acids [15]. Point mutations were identified in

Fig. 1A. MR/CT imaging of fatty degenerative change in lower leg muscles. Genes causing predominant involvement of anterior compartment muscles: tibialis anterior, extensor hallucis longus and extensor digitorum longus.

Fig. 1B. MR/CT imaging of fatty degenerative change in lower leg muscles. Genes causing predominant involvement of posterior compartment calf muscles: gastrocnemius medialis, gastrocnemius lateralis and soleus.

Fig. 1C. MR/CT imaging of fatty degenerative change in lower leg muscles. Genes causing involvement of both anterior, lateral and posterior compartment muscles are the C-terminal Filamin-C mutations causing myofibrillar myopathy and alphaB-crystallin, but also the established distal myopathies Welander disease and the MPD3 [58] without yet identified genes this pattern is common.
unrelated French and Belgian TMD families [24,25], truncating mutations in the last and second to last exons of titin in Spanish and French families [26], and recently point mutations in the last exon in an Italian TMD family [27] and one Swiss patient as reported here. Sequencing the last three titin exons is the diagnostic method of choice in new families without Finnish ancestry.

2.1.3. ZASPopathy (Markesbery–Griggs late onset distal myopathy)

Symptoms start after age 40–50 years with ankle weakness, progressing slowly to involve finger and wrist extensors. Mild-moderate proximal weakness occurs very late, but in the severe case walking is lost 15 or 20 years after onset. Very late cardiomyopathy and heart block requiring a pacemaker has been reported [7]. CK levels are normal or mildly elevated and muscle MRI shows early degenerative changes in medial gastrocnemius and soleus (Fig. 1B). At the late stage all lower leg muscles are replaced while proximal lower limb muscles show mild changes. Myofibrillar abnormalities with rimmed and non-rimmed vacuoles are shown on muscle biopsy with dark and hyaline structures in trichrome stain corresponding to myofibrillar disintegration on EM. Protein aggregations contain ectopic dystrophin, desmin, myotilin, alphaB-crystallin, among others [18].

2.1.3.1. Epidemiology. So far, all reported families are of Central European descent.

2.1.3.2. Molecular genetics. Mutations in ZASP (Z-disk alternatively spliced PDZ-domain containing protein, also termed LDB3 gene) are responsible with two ancient European founder mutations, A165V and A147T, being most prevalent [18].

2.1.4. Distal myotilinopathy

Weakness of ankle plantar- or dorsiflexion starts late, between age 50 and 60 [28]. Despite the very late onset disease progression can be very disabling. Upper limbs and proximal leg muscle weakness with loss of ambulation may occur after 10 years [29,30]. CK levels vary from normal to slight increase. Muscle MRI show fatty degenerative changes first in calf muscles followed by all lower leg muscles and much milder involvement of proximal lower limb muscles (Fig. 1B). Muscle pathology is myofibrillar and similar to that of ZASPopathy, including ultrastructure [31], and may contain pathologically defined spheroid bodies [32].

2.1.4.1. Molecular genetics. Myotilin mutations were first described in two families with dominant limb-girdle phenotype (LGMD1A). However, our and other experience suggest that most myotilinopathy patients present with late onset distal myopathy [29,33]. Almost all myotilin mutations are located within the second exon, coding for a serine-rich domain of the Z-disk protein.

2.1.5. Vocal cord and pharyngeal distal myopathy (VCPDM, MPD2)

Late onset distal upper and lower extremity weakness combined with symptoms of vocal cord and pharyngeal weakness characterize this disease. Distal weakness may start either in ankle and toe extensors or in finger extensors. Serum CK levels reported to be normal or up to eightfold increased and muscle biopsy findings consist of rimmed vacuolated fibers [34]. Muscle imaging has not been reported.

2.1.5.1. Molecular genetics and epidemiology. The disease is so far known only in two families, one US family and one
Bulgarian family. Both unrelated families were shown to have the same missense mutation in a protein of the nuclear matrix, Matrin3\[35\].

2.1.6. VCP-mutated distal myopathy

VCP mutation may cause a late onset distal myopathy clinically indistinguishable from WDM or TMD [36], even if proximal or scapuloperoneal myopathy with Paget, and frontotemporal dementia (IBMPFD) is more common [37]. In the reported distal family Paget disease was not present, the myopathy was slowly progressive but remained distal, and rapidly progressive lethal frontotemporal dementia appeared very late, 20–25 years after onset. CK level were slightly elevated, muscle biopsy showed rimmed vacuolation with ring fibers and muscle CT/MRI anterior compartment fatty degeneration in lower legs (Fig. 1A).

2.1.7. Alpha-B crystalline-mutated distal myopathy

Distinct late onset distal myopathy without cardiomyopathy, respiratory dysfunction or significant cataracts may occur with CRYAB mutations [38]. CRYAB mutations have previously been associated with distal and proximal muscle weakness combined with cataracts and dilated cardiomyopathy [39]. Muscle biopsy showed rimmed vacuolar pathology.

2.2. Adult onset dominant distal myopathies

2.2.1. Desminopathy

Juvenile or early adult onset distal leg weakness, especially when combined with cardiomyopathy and/or respiratory failure should alert the clinician to consider desmin gene, CK levels are moderately elevated and muscle biopsy findings are usually consistent with myofibrillar myopathy. However, typical myopathy may be inconsistent as shown in the scapuloperoneal syndrome of Kaeser reported first to be a neurogenic disease [40]. Muscle MRI displays earliest changes in the anterior compartment of lower legs with progression to other distal and proximal muscles (Fig. 1A).

2.2.1.1. Molecular genetics.

Mutations are located over large parts of the gene with no certain genotype-phenotype correlation.

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**Table 2**

Distal phenotypes occurring with other diseases.

<table>
<thead>
<tr>
<th>Disease</th>
<th>Age of onset</th>
<th>Inheritance</th>
<th>ON</th>
<th>Off</th>
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<tbody>
<tr>
<td>FSHD</td>
<td>Childhood to early adulthood</td>
<td>AD/spor</td>
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<tr>
<td>Myotonic dystrophy type 1</td>
<td>Late</td>
<td>AR/spor</td>
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<tr>
<td>DNM2 mutated centronuclear myopathy</td>
<td>Late</td>
<td>AR/spor</td>
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<tr>
<td>Metabolic myopathies</td>
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<td>AD</td>
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<tr>
<td>Branching glycogenosis</td>
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<td>Debrancher glycogenosis</td>
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<tr>
<td>Phosphorylase b kinase deficiency</td>
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<tr>
<td>PNPLA2 lipidosis</td>
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<tr>
<td>Caveolinopathy</td>
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<tr>
<td>Telothelinopathy</td>
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<tr>
<td>Nemaline myopathy</td>
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<tr>
<td>Sporadic inclusion body myositis s-IBM</td>
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<tr>
<td>Scapuloperoneal syndromes</td>
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<tr>
<td>Distal spinal muscular atrophy</td>
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<tr>
<td>Focal motor neuron disease (e.g., Hirayama)</td>
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**Fig. 2B.** Flow chart algorithm for diagnostic purpose aiming at reducing the number of genes qualified for possible molecular genetic testing, using clinical data as the starting point. (adapted from Udd: 165th ENMC International Workshop: Distal myopathies) [60].
2.2.2. Distal ABD-filaminopathy

This is one of the newcomers with a distinct clinical onset of weakness first of the handgrip in early adulthood followed by thenar atrophy and calf muscle weakness in the 40’s. [41]. CK is normal or slightly elevated. Muscle biopsy shows non-specific pathology, unlike the myofibrillar and rimmed vacuolated pathology described with FLNC mutations causing generalized myofibrillar myopathy. Muscle CT/MRI on lower limbs reveals replacement in all posterior calf muscles while anterior and lateral compartments are spared (Fig. 1B).

2.2.2.1. Molecular genetics and epidemiology. Mutations in the N-terminal actin binding domain (ABD) of muscle specific Filamin C are the underlying cause of this particular type of distal myopathy, whereas in the clinically and pathologically different myofibrillar myopathy mutations are located in the central or C-terminal part [42]. Currently one Australian and two Italian families are known.

2.3. Early onset dominant distal myopathies

2.3.1. Laing distal myopathy (MPD1)

Weakness of ankle dorsiflexion, neck flexors and a hanging big toe usually appear in early childhood (see also MRI findings in Fig. 1A). Progression is slow, most patients remain ambulant, and weakness of finger extensors, shoulder muscles, scoliosis and milder proximal weakness may occur [8]. Muscle biopsy shows findings compatible with congenital fiber type disproportion. Rimmed vacuoles are exceptional with some mutations. CK levels are normal or mildly elevated [43].

2.3.1.1. Epidemiology. Families and sporadic de novo-mutated patients are known in very many populations, and based on experience from Finland, Spain and Norway the prevalence is >1/million [44,45].

2.3.1.2. Molecular genetics. MYH7 gene encoding slow beta myosin heavy chain protein is the main myosin isoform in type 1 slow muscle fibers and in the heart. Cardiomyopathy is only occasionally part of the phenotype in Laing distal myopathy. All mutations causing this phenotype are located in the tail region of the MYH7 heavy chain, with hot-spots and many occurring de novo [17,45].

2.3.2. KHLH9-mutated distal myopathy

Weakness of ankle dorsiflexion in the so far only known one German family starts in early childhood. Later patients have atrophy of intrinsic hand muscles and proximal limb weakness [46].

EMG is myopathic and muscle biopsy findings are myopathic without rimmed vacuoles. CK levels are mildly-moderately elevated.

2.3.2.1. Molecular genetics. KHLH9 gene encodes a kelch-like homologue protein [46].

2.4. Early onset recessive distal myopathies

2.4.1. Distal nebulin myopathy

Onset of ankle dorsiflexion is usually in childhood with weakness of extensors of fingers and hands. Neck flexors weakness is less marked than in Laing myopathy. The progression is slow and patients remain ambulant [47]. EMG is myopathic or shows mixed findings. CK is normal or mildly elevated. Selective fatty degeneration in the lower leg anterior compartment muscles is typically present on muscle CT/MRI (Fig. 1A). Muscle biopsy findings are problematic and may show scattered and grouped atrophic fibers mimicking neurogenic changes without nemaline rods on light microscopy. On EM rare small rod structures may be encountered [47].

2.4.1.1. Molecular genetics. This mild distal myopathy is caused by two missense mutations in nebulin [47], while disruptive recessive mutations cause the more severe congenital nemaline myopathy.

2.5. Early adult-onset distal myopathies

2.5.1. GNE-myopathy (Nonaka myopathy, Distal myopathy with rimmed vacuoles)

The disease, first described in Japanese patients, presents with weakness of ankle dorsiflexors and toe extensors in the second or third decade, followed by foot drop and a step-page gait (see also CT findings in Fig. 1A). Proximal weakness with relative sparing of quadriceps muscles are the next stages and patients may become wheelchair-dependent 10 to 15 years after onset [4]. EMG is myopathic with spontaneous activity and CK is moderately increased (3-4-fold). On muscle pathology abundant rimmed vacuoles are found also in proximal muscle.

2.5.1.1. Epidemiology. Founder mutations account for higher frequency in Japanese and Middle Eastern populations, whereas the general stochastic frequency of mutations indicates a prevalence of less than 1/million.

2.5.1.2. Molecular genetics. The gene responsible for disease is UDP-N-acetylgalactosamine 2 epimerase/N-acetyl mannosamine kinase (GNE) and was first identified in patients in Middle East described as having quadriceps sparing myopathy (HIBM) [48]. Later the same gene was confirmed in Nonaka myopathy [16]. GNE is the rate limiting enzyme for sialic acid and hyposialylation is proposed as one pathomechanistic feature currently targeted for therapeutic approach.

2.5.2. Miyoshi myopathy (MM)

Calf muscles are first affected with weakness and atrophy between 15 and 25 years [2,3] (see also MRI findings Fig. 1B). Proximal limb muscles are always involved later, and the two phenotypes of dysferlinopathy, Miyoshi myopathy and LGMD2B, converge by time [49,50]. Rarely, the anterior lower leg muscles are affected at onset [51]. Charac-
teristic for the disease are very high CK levels ranging from 20 to 150 fold normal values. EMG shows myopathic changes with spontaneous activity due to fiber necrosis seen on muscle pathology together with other dystrophic changes. Gold standard for diagnosis relies on absent dysferlin on immunohistochemical staining of muscle sections or on Western blotting tissue of muscle or monocytes.

2.5.2.1. Epidemiology. Patients were first described in Japan. Later experience show that patients exist in many populations with an overall frequency of dysferlinopathies of around 1/million.

2.5.2.2. Molecular genetics. Mutations in the dysferlin gene cause both distal Miyoshi myopathy and proximal onset LGMD2B [13]. Dysferlin has been implicated to be important for sarcolemmal repair mechanisms.

2.5.3. Distal anoctaminopathy

Anoctaminopathy may present with various phenotypes, one of them being early adult onset distal myopathy with asymmetric calf involvement, starting with pain and hypertrophy turning into weakness and atrophy a few years later (see also MRI findings Fig. 1B) [52]. Similar to MM, patients have the very high CK levels and nonspecific dystrophic myopathology with just scattered fiber necrosis. The evolution is slow and patients remain ambulant until high age.

2.5.3.1. Molecular genetics and epidemiology. ANO5 (TMEM16E) codes for a calcium-activated chloride channel protein anoctamin-5, but the role of this molecule in muscle is not known. Anoctaminopathy seems to be one of the most common causes of muscular dystrophy with mutations spread all over the gene [53]. Diagnosis is currently made by molecular genetics as the protein identification in muscle is not available.

2.6. Other distal myopathies

Juvenile onset sporadic/recessive oculopharyngodistal myopathy has been described in a few reports and certainly represents a distinct entity. This is also true for adult onset dominant oculopharyngeal distal myopathy, even if the molecular genetics is unsettled. Recently a large number of both recessive and dominant families from Turkey were reported [54].

A number of distal myopathies have been reported in single families and shown to be distinct from any of the other known entities by molecular genetic linkage at the time of study:

- Distal neuromyopathy with pes cavus (MIM 601846) [55].
- Autosomal dominant distal myopathy in a Polish-USA family [56].
- Adult onset dominant distal myopathy (Fig. 1C), MPD3 (MIM 610099) [57,58].
- Later onset recessive calf distal myopathy [59].

3. Management

The final genetic diagnosis is necessary to avoid wrong treatments due to erroneous diagnosis (Figs. 2A and 2B). In desminopathy associated cardiomyopathy and respiratory muscle involvement needs correct monitoring. In the case of VCP mutated distal myopathy Paget disease cannot be excluded even if it was not present in the primary distal myopathy family, and late dementia is a lethal complication. In the milder late onset forms orthoses are commonly used for stabilization of wrists, fingers, ankles and toes. In cases of early severe foot drop tibialis posterior tendon reposition has been used in both TMD and VCP mutated distal myopathy patients with good outcome for many years. However, validated studies of the benefit of these measures are not available.

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