Distal myopathies are a group of heterogeneous disorders classified into one broad category due to the presentation of weakness involving the distal skeletal muscles. The recent years have witnessed increasing efforts to identify the causative genes for distal myopathies. The identification of few causative genes made the broad classification of these diseases under “distal myopathies” disputable and added some enigma to why distal muscles are preferentially affected. Nevertheless, with the clarification of the molecular basis of specific conditions, additional clues have been uncovered to understand the mechanism of each condition. This review will give a synopsis of the common distal myopathies, presenting salient facts regarding the clinical, pathological, and molecular aspects of each disease. Distal myopathy with rimmed vacuoles, or Nonaka myopathy, will be discussed in more detail.

Key words: Amyloid, hIBM, sialic acid

### Introduction

Although proximal muscles of the extremities are predominantly affected in most primary myopathies including muscular dystrophies, there are several diseases preferentially involving distal muscles from the early stage of the disease and thus have been labeled as distal myopathies. Classification of the distal myopathies was therefore a matter of dispute; most in the past were classified on the age of onset of the disease and mode of inheritance,[1-5] though recent studies have shown a large list of diseases based on molecular biologic aspects.[6] Despite that the term “distal myopathy” may not be exactly accurate, as some conditions included in this classification actually are characterized by dystrophic changes in the muscle, it is maintained for historical purposes and clinical classification.

Since the discovery of the gene loci for a number of distal myopathies, several diseases previously categorized as different disorders have now proven to be the same or allelic disorders (e.g. distal myopathy with rimmed vacuoles and hereditary inclusion body myopathy, Miyoshi myopathy and limb-girdle muscular dystrophy type 2B (LGMD 2B)).

This review will focus on the most commonly known and distinct distal myopathies, using a simple classification: distal myopathies with known molecular defects [Table 1] and distal myopathies with unknown causative genes [Table 2]. The identification of the genes involved in distal myopathies has broadened this classification into sub-categories as to the location of encoded proteins; sarcomere (titin, myosin); plasma membrane (dysferlin, caveolin); cytoskeleton (rare; includes desmin, myotilin, αB-crystallin, ZASP, filamin C, nebulin); and cytosol (GNE).

### Tibial Muscular Dystrophy (late onset, Type 2)

**Clinical and pathologic characteristics**

Udd et al.[7] first reported 66 patients from several Finnish families who had an autosomal dominantly inherited late adult onset distal leg myopathy with weakness confined mainly to the anterior tibial muscles. They named the disorder tibial muscular dystrophy (TMD), because they thought that the muscle pathology was similar to that seen in muscular dystrophy, including muscle fiber necrosis and fat tissue replacement, but serum creatine kinase (CK) levels were normal or slightly elevated.

The clinical phenotype presents after the age of 35 years, with almost selective involvement of the anterior tibial muscles and long toe extensors initially, resulting in moderate foot drop in 10-20 years. The disease severity varies from the absence of symptoms to marked difficulty in walking. Weakness may initially be
### Table 1: Distal myopathies with identified causative genes

<table>
<thead>
<tr>
<th>Disease</th>
<th>Onset</th>
<th>Weakness at initial presentation</th>
<th>CK</th>
<th>Gene</th>
<th>Locus</th>
<th>Inheritance pattern</th>
</tr>
</thead>
<tbody>
<tr>
<td>Udd distal myopathy / Udd muscular dystrophy (TMD)</td>
<td>2-15</td>
<td>Anterior lower leg</td>
<td>Normal to 4x elevated</td>
<td>TTN (titin)</td>
<td>2q31</td>
<td>AD</td>
</tr>
<tr>
<td>Tibial muscular dystrophy (TMD)</td>
<td>2-15</td>
<td>Anterior lower leg</td>
<td>Normal to 3x elevated</td>
<td>NEB (nebulin)</td>
<td>2q22</td>
<td>AR</td>
</tr>
<tr>
<td>Distal nebulin myopathy</td>
<td>35</td>
<td>Anterior lower leg</td>
<td>Normal to 8x elevated</td>
<td>MH7 (slow skeletal/ beta cardiac myosin)</td>
<td>14q12</td>
<td>AD</td>
</tr>
<tr>
<td>Laing distal myopathy</td>
<td>early</td>
<td>Hands</td>
<td>Moderately to 100x elevated</td>
<td>DYSF (dysferlin)</td>
<td>2p13.3-p13.1</td>
<td>AR</td>
</tr>
<tr>
<td>Myoshi myopathy</td>
<td>15-30</td>
<td>Posterior lower leg, calf</td>
<td>3x to 10x elevated</td>
<td>CAV3 (Caveolin-3)</td>
<td>3p25</td>
<td>AD</td>
</tr>
<tr>
<td>Distal caveolinopathy</td>
<td>early</td>
<td>Hands</td>
<td>Normal to 5x elevated</td>
<td>GNE (UDP-N-acetylglucosamine 2-epimerase/N-acetylmannosamine kinase)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonaka/DMRV/IBM2</td>
<td>15-30</td>
<td>Anterior lower leg</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Desminopathy MFM</td>
<td>15-40</td>
<td>Distal leg and forearm + cardiomyopathy</td>
<td>Normal to 3x elevated</td>
<td>DES (desmin)</td>
<td>9p12-p11</td>
<td>AR</td>
</tr>
<tr>
<td>Myotilinopathy MFM</td>
<td>40-60</td>
<td>Lower legs and hands</td>
<td>Normal to 3x elevated</td>
<td>MYOT (Myotilin/TTID)</td>
<td>2q35</td>
<td>AD, sporadic</td>
</tr>
<tr>
<td>Alpha-B crystallinopathy MFM</td>
<td>adult</td>
<td>Distal leg and hands + cardiomyopathy</td>
<td>Variable</td>
<td>CRYAB (α-B crystallin)</td>
<td>5q31</td>
<td>AD</td>
</tr>
<tr>
<td>ZASP-related MFM</td>
<td>40-60</td>
<td>Lower legs and hands</td>
<td>Normal to 3x elevated</td>
<td>LDB3/2ASP (Z-band alternatively spliced PDZ motif containing protein)</td>
<td>11q22.3-q23.1</td>
<td>AD</td>
</tr>
</tbody>
</table>

#### Laing Distal Myopathy

Laing distal myopathy (MDM1) was originally described by Laing et al. [14] as an autosomal dominant distal muscular dystrophy. It is a distinct condition characterized by weakness and atrophy of the distal muscles, similar to the clinical features of other distal myopathies. However, Laing distal myopathy has a more pronounced distal involvement and may present with a milder phenotype compared to other distal myopathies.

The gene in MDM1 has been mapped to Chromosome 3q21 and mutations were found in a gene encoding a structural protein titin. The gene responsible for this disease was initially found in the Finnish population, but subsequent studies have shown that this disease is also found in the French and Belgian populations. The titin gene is large and contains many exons, and mutations in this gene have been associated with distal myopathy.

#### Molecular aspects

The gene in MDM1 has been mapped to Chromosome 3q21. Mutations in the DMDM1 gene were found in patients with distal myopathy, indicating that this gene is a potential cause of the disease. The protein encoded by the DMDM1 gene is a large, structurally complex protein that is involved in the regulation of muscle fiber size and strength. Mutations in this gene may disrupt the function of this protein, leading to the development of distal myopathy.

#### Clinical and pathologic characteristics

Distal myopathies such as Laing distal myopathy are characterized by weakness and atrophy of the distal muscles, including the muscles of the lower legs and hands. The disease onset is usually between 4 and 5 years of age, and the disease progression is slow, with symptoms typically developing gradually. Elderly patients are usually ambulant, and the disease is usually not associated with life-threatening complications. Therefore, it is important to identify and treat the underlying cause of distal myopathies to improve the quality of life and management of affected individuals.
affecting the anterior compartment of the lower leg and selective involvement of the toe extensors, giving rise to the characteristic hanging big toe sign. The disease is slowly progressive, i.e. a patient has been reported to maintain independent ambulation 23 years after the initial investigation, whereby patients gradually develop weakness of finger flexors and proximal muscles including neck flexors, shoulder, trunk, facial and tongue muscles. Cardiomyopathy is rare and severe respiratory problems have not been described. Serum CK levels are mildly elevated.

The pathological features are variable and there are no pathognomonic diagnostic features. In general, fiber size distribution appears to be bimodal. Type I fibers are atrophic in 50% of the population and express both slow- and fast-type myosin. In tibialis anterior muscles, virtually all muscles abnormally express fast-type myosin. RVs are found in a minority of patients with MPD1, but not prominent. Immunohistochemical staining for slow and fast myosin showed co-expression of slow and fast myosin in some Type I fibers, possibly indicating fiber type switching. This finding seems to be a useful aid to diagnosis.

**Molecular aspects**

The gene for this myopathy is mapped to chromosome 14 and the mutations are found in the slow myosin heavy chain gene MYH7, hence it is sometimes known as myosinopathy. Mutations have been discovered on the MYH7 tail region, which is physically located in the M-line of the sarcomere, and where it was described to interact with myomesin and titin. Mutations in MYH7 have also been reported in patients with hylane body myopathy, suggesting that this myopathy is allelic with myosinopathy.

**Distal Nebulin Myopathy**

**Clinical and pathological characteristics**

Recently, four families of Finnish decent were described to have an early onset distal myopathy with remarkable involvement of the ankle dorsiflexors (foot drop); other muscles severely involved include finger extensors and neck flexors. In some of the older patients, mild proximal muscle weakness was noted. Moderate facial weakness was seen in few patients.

The muscle biopsy can generally be described as myopathic, although the severity of the pathology varied remarkably. Chronic atrophy was suggested by the presence of large hypertrophic fibers with increase in internal nuclei and nuclear clumps that express neonatal MHC. Nemaline bodies were not observed on light microscopy histochemistry, but were seen in toluidine blue-stained semi-thin epon sections of some patients.

**Molecular aspects**

Extensive analysis of patients revealed an abnormal SSCP band in the nebulin gene (NEB), in two of the four families. Gene sequencing revealed homozygous mutations in NEB. This was rather surprising because recessive mutations in NEB have been associated with nemaline myopathy, clinical picture of which is similar to that of most congenital myopathy and presents with proximal myopathy. Actually, in nemaline myopathy, most of the mutations identified were either nonsense, frameshift, or splice-site mutations, while mutations in the distal myopathy phenotype are missense. Thus Wallgren-Pettersson et al. concluded that homozygosity for NEB missense mutations causes a distinct type of recessively inherited distal myopathy, albeit rarely.

**Autosomal Recessive distal Muscular Dystrophy**

(Miyoshi myopathy; early adult onset, Type 2)

**Clinical and pathological characteristics**

Miyoshi myopathy (MM) is an adult-onset autosomal recessive condition characterized by preferential gastrocnemius muscle involvement and dystrophic muscle pathology. MM seems to be widely distributed throughout the world, because many
similar patients have been described from various countries.\textsuperscript{20–22}

The symptoms and the onset of the disease can be variable, but most patients become aware of difficulty in walking in early adulthood, from 20 to 40 years. In the early stages of the disease, patients have muscle atrophy and weakness in the distal parts of legs, predominantly of the gastrocnemius and soleus muscles, and therefore have difficulty in standing on tip-toe. The disease subsequently progresses rather rapidly and muscle atrophy/weakness becomes more prominent and may spread to the proximal muscles. A few patients become non-ambulant 10-20 years after onset of the disease. Cardiac and respiratory muscles are not involved. Serum CK levels are elevated to 20-100 times the normal value. Muscle computed tomography (CT) shows preferential soleus, gastrocnemius and occasionally paraspinal muscle involvement. Despite the characteristic involvement of the posterior lower leg muscles, there is a variant of MM which peculiarly involved the tibialis anterior among a Spanish population, and hence was called distal myopathy with anterior tibialis involvement (DMAT).\textsuperscript{[23]}

Muscle biopsies show dystrophic changes with active fiber necrosis and regeneration, interstitial fibrosis, and fat tissue replacement,\textsuperscript{[18,19]} similar to those seen in Duchenne or limb-girdle muscular dystrophy. Inflammatory cellular infiltration is commonly seen and could sometimes lead to misdiagnosis of polymyositis.\textsuperscript{[24]}

\textbf{Molecular aspects}

The causative gene is DYSF gene in Chromosome 2p13.\textsuperscript{[25]}

Mutations are variable and include insertions, deletions, altered splicing and point mutations. The exact function of dysferlin remains unknown, but it is thought to allow rapid membrane resealing of membranes disrupted by mechanical stress. Interestingly, patients with LGMD2B with gene locus at 2p13 also have mutations in DYSF, suggesting heterogeneous phenotypic expressions in the DYSF gene mutations.\textsuperscript{[26]} This is not surprising, because MM patients occasionally show apparent proximal muscle involvement as the disease advances.

\textbf{Caveolinopathy}

\textbf{Clinical and pathological characteristics}

Caveolinopathy is known to cause LGMD1C, however, other phenotypes have been associated with this condition, including distal myopathy, rippling muscle disease, and hyperCKemia.\textsuperscript{[27]} In the initial report of this caveolinopathy-associated distal myopathy, onset of weakness and atrophy was at 12 years of age, mainly involving the intrinsic muscles in the hands and feet, without involvement of the proximal muscles. The progression was slow. Muscle biopsy showed mild variation in fiber size, increased number of internalized nuclei, and predominance of Type 1 fibers.

\textbf{Molecular aspects}

The causative gene is CAV3, which encodes a protein that is implicated in the development of the T-tubule system in the skeletal muscle. Mutations are mostly heterozygous missense mutations, but one deletion mutation was also identified. Like in all caveolinopathies, the expression of caveolin 3 is reduced, however, it should be noted that caveolin 3 expression can also be secondarily reduced in some muscular dystrophies like sarcoglycanopathies and dystrophinopathies, underscoring the importance of genetic screening for final diagnosis.

\textbf{Myofibrillar Myopathy}

The term myofibrillar myopathy (MFM) was proposed by AG Engel’s group in 1996 as a non-committal term for a pathologic pattern of myofibrillar dissolution associated with accumulation of myofibrillar degradation products and ectopic expression of multiple proteins including desmin, αB-crystallin, dystrophin and amyloid material.\textsuperscript{[28,29]} This condition had previously been labeled as spheroid body myopathy, cytoplasmic body myopathy, Mallory body myopathy and desmin storage myopathy, among other names. In this review, some MFMs are included as patients can present with distal weakness, but it is important to note that both distal and proximal muscles can be involved.\textsuperscript{[30]} In patients with MFM, mutations were found in DES (desmin), CRYAB (αB-crystallin), MYOT (myotilin), LDB3 (Z-band alternatively spliced PDZ-containing protein; ZASP), and FLNC (filamin C). Accordingly, although MFM is morphologically distinct it is genetically and clinically heterogeneous.\textsuperscript{[30]}

Only two of 63 patients had distal myopathy. Most patients with mutations in DES had dilated cardiomyopathy and generalized muscle weakness.\textsuperscript{[31]} Although many patients with distal myopathy with desmin accumulation have been reported in the literature,\textsuperscript{[32]} they were probably not common in desmin myopathy with DES mutation.

Distal dominant involvement seems to be rare in patients with CRYAB\textsuperscript{[33]} and ZASP\textsuperscript{[34]} mutations. Interestingly, a family with autosomal dominantly inherited distal myopathy first described by Markesbery \textit{et al.}\textsuperscript{[35]} is now known to be caused by the ZASP mutation A165V.\textsuperscript{[36]} Haplotype studies in this family and in five other families with European ancestry carrying the identical A165V mutation share common markers at the locus suggesting the existence of a founder mutation. Further study is necessary to determine whether ZASP
gene mutation commonly causes distal myopathy.

MYOT, the gene associated with autosomal dominantly inherited LGMD1A,[37,38] also causes distal myopathy.[39-42] Myotilin (myofibrillar protein with titin-like Ig domain) is a 57 kDa Z-disc component that interacts with alpha-actinin, filamin-C, FATZ (calsarcin) and actin. The onset of distal myopathy with myotilin gene mutation is in late adulthood ranging mostly from 50-75 years of age. In the lower legs, the soleus and gastrocnemius muscles are predominantly involved from the early stage,[40,41] extending to the anterior compartment with disease progression.[42] Electromyogram shows myopathic pattern with occasional neurogenic components. Serum CK levels are normal to slightly elevated.

**Distal Myopathy with Rimmed Vacuoles (DMRV; Nonaka; early adult onset, Type 1)**

Among the various forms of distal myopathies, DMRV has been regarded as a distinct disorder from both the clinical and pathologic aspects.[43-45] The disease is inherited as an autosomal recessive trait and characterized clinically by preferential muscle involvement of the anterior compartment of the lower legs, i.e. tibialis anterior muscle, beginning in young adulthood, and pathologically by the presence of RVs in muscle biopsies. We thought that distal muscle involvement was the initial important disease process, but Argov et al.[46] thought quadriceps sparing was the unique finding because the bulk and strength of quadriceps muscles were relatively preserved even in the advanced stages. Since pathologic findings are similar to sporadic inclusion body myositis (sIBM), Askanas et al. suggested the term “hereditary inclusion body myopathy (hIBM)” for these patients.[47,48] Subsequently, the term hIBM has been widely used usually when discussing the pathologic findings and DMRV when referring to patients clinically.

**Clinical and pathologic findings**

The age at onset of the disease ranges from 15 to 40 years, averaging 26 years.[43,45] Since the tibialis anterior muscle is preferentially involved from the early stage [Figure 1], the initial symptom is gait disturbance, usually with difficulty in climbing stairs and running. The disease is rather rapidly progressive.[48,49] Patients become non-ambulant between 26 and 57 years, average of 12 years after the onset of the disease.[43,49] Cardiac and respiratory muscles are less involved. Although the anterior tibial muscle is most significantly affected, gastrocnemius, hamstrings, paraspinal and sternocleidomastoid muscles are also involved from an early stage when one examines muscles by CT [Figure 2A and B]. Even in the advanced stages, quadriceps muscles are relatively spared [Figure 2C]. Serum CK levels are normal to mildly elevated.

In all muscle biopsies, there are myopathic changes with variation in size in both Type 1 and 2 fibers. RVs are present predominantly in atrophic fibers which are occasionally aggregated forming small groups [Figure 3A].[43,45] Necrotic and regenerating fibers can
be rarely seen. Type 1 fibers tend to predominate as the disease progresses.\[^{43}\]

**Process of muscle fiber degeneration**

RV formation is thought to be the primary pathologic event which induces muscle fiber atrophy and loss in DMRV, but its exact significance remains uncertain. By electron microscopy, the RV consists of autophagic vacuoles and myeloid bodies [Figure 3B]. In the vicinity of the RVs, myofibrils are frequently disorganized, therefore degenerated contractile proteins and other cytoplasmic debris appear to activate the lysosome (autophagosome) to scavenge them.\[^{50,51}\] In the myofibrillar degeneration pathways, non-lysosomal ATP-ubiquitin proteasome proteolysis was proposed to play a role as there is increased proteasome activity in and around RVs.\[^{52}\] The RV itself is not specific for DMRV, but is also found in other disorders, including chronic muscular dystrophies, metabolic disorders, myotonic dystrophy,\[^{45,53}\] oculopharyngeal muscular dystrophy, oculopharyngodistal myopathy, and Marinesco-Sjögren syndrome.\[^{45}\]

RVs in muscle fibers in sIBM\[^{48}\] and DMRV\[^{54}\] occasionally contain congophilic deposits, which are also positively stained with β-amyloid protein precursor and tau protein antibodies.\[^{48,53}\] This notion is further supported by the finding in the DMRV model mouse: amyloid deposits preceded myofibrillar degeneration and accumulation of the autophagic vacuoles suggesting that the autophagic phenomenon is not a primary pathologic event in DMRV.\[^{55}\]

A common pathologic feature includes various nuclear inclusions and tubulofilamentous inclusions measuring 15-20 nm [Figure 4A] which are similar to 8-10 nm inclusions in oculopharyngeal muscular dystrophy. The nuclei with such inclusions are sometimes markedly degenerated and are surrounded by degenerated myofibrils, suggesting that nuclear degeneration precedes myofibrillar degeneration and autophagic phenomenon [Figure 4B]. Because some nuclei are stained positively with the TUNEL method, the nuclear change is thought to be related to apoptosis.\[^{56}\]

A close relationship between nuclear change and RV formation has been suggested. In autosomal dominant inclusion body myopathy with Paget’s disease of bone and frontal dementia (IBMPFD), mutations were

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**Figure 3:** Typical muscle pathology seen in DMRV. Modified Gomori trichrome stain (A) shows moderate variation in fiber size with numerous rimmed vacuoles in atrophic fibers (arrows). On electron microscopy (B), rimmed vacuoles are actually clusters of autophagic vacuoles (arrows) and numerous myeloid bodies; markedly disorganized myofibrils are seen (asterisk). Scale bar in (B) denotes 1.0 micron.

**Figure 4:** Pathologic hallmarks of DMRV on electron micrograph. Tubulofilamentous nuclear inclusions measuring 15-20 nm in diameter are usually seen in fibers with rimmed vacuoles (A); bar denotes 0.2 micron. In figure (B), myofibrillar degeneration (asterisk) and autophagic phenomenon are seen in the vicinity of an abnormal nucleus (N) filled with tubulofilamentous inclusion, suggesting a close relationship between nuclear change and myofibrillar degeneration; bar denotes 1.0 micron.
found in valosin-containing protein (VCP). The VCP is a polyglutamine (polyQ) interacting protein and co-localizes with ubiquitin-containing inclusions in a number of neurodegenerative disorders including polyQ diseases, Parkinson, Alzheimer and Creutzfeldt-Jakob diseases. Although nuclear inclusions in polyQ diseases are different from those in DMRV, nuclear degeneration probably precedes cytoplasmic vacuolar changes resulting in cell death (and probably apoptosis).

Molecular aspects
The gene for hIBM was first mapped to Chromosome 9 in 1996 and in DMRV in 1997. The most epoch-making event in hIBM was the discovery of mutations in UDP-N-acetylglucosamine 2-epimerase/N-acetylmannosamine kinase (GNE), a gene involved in sialic acid synthesis. GNE consists of an epimerase domain and a kinase domain (Figure 5). The identification of GNE mutations among Japanese DMRV patients confirmed that DMRV and hIBM are the same disorders. Almost all of the mutations associated with DMRV/hIBM are missense mutations scattered throughout the open reading frame and can be found either in the epimerase domain only, in the kinase domain only, or heterozygous mutations on each domain (Figure 5).

The most common 2186T-to-C (M712T) mutation was initially thought to be restricted to Middle Eastern Jews including a large proband family analyzed by Dr Argov’s group. On the other hand, the most frequent mutation in Japanese DMRV patients was the 1714C-to-G (V572L) mutation which was found in more than 50% of patients. To date, several mutations have also been reported in other populations throughout the world.

Genotype and phenotype correlation
Although homozygous V572L mutation was thought to present with the typical clinical features of DMRV, further study is necessary to clarify the genotype/phenotype correlation. A previous study reported that there was an unusual patient with proximal muscle weakness. Furthermore, we had an individual with a homozygous M721T mutation with no muscle symptom, suggesting an incomplete penetrance of the disease.

Two patients had inflammatory cellular infiltration in muscle biopsies mimicking the pathology of sIBM. The onset of DMRV is in young adulthood while sIBM becomes manifest after 50 years, therefore one can differentiate the two diseases with little difficulty although there may be patients with late onset DMRV with inflammation among patients clinically diagnosed as having sIBM.

Biochemical abnormalities
The GNE enzyme is a bifunctional enzyme catalyzing two initial steps in the biosynthesis of sialic acid. Sialic acids are present at the terminal ends of glycolipid or glycoprotein on the cell surface, and are thought to contribute to glycoprotein stability, in addition to other various cellular functions. Since GNE knockout is lethal in the mouse embryo this suggests that the GNE plays a crucial role in organ synthesis. Moreover, as GNE is ubiquitously expressed, mutations in the gene are thought to induce more serious disorders than DMRV in which only the muscle is affected. Nevertheless, the epimerase activity in patients was markedly reduced in white blood cells and lymphoblastoid cell lines, suggesting that the mutations are responsible for decreased or loss of the GNE gene function. It should be noted that most mutations are missense, thus a complete loss of enzyme function may not be expected.

Altered cellular sialylation has been controversial. Hinderlich et al. found no abnormalities in patient-derived lymphoblastoid cell lines with the M712T mutation, although Noguchi et al. found sialic acid levels reduced to 60-70% of control in biopsied and cultured muscle cells, and variable lectin binding reactivities from fiber to fiber. Other reports also described defective glycosylation of skeletal muscle glycoproteins, including α-dystroglycan which is known to be a hyperglycosylated cell membrane protein. The concept of hyposialylation was further supported by the only existing model of DMRV, the Gne knockout mouse expressing human GNE D176V mutation, wherein marked hyposialylation in serum, muscle and other organs was seen.

It is still unknown how GNE mutations induce nuclear inclusion bodies and degeneration followed by amyloid accumulation and myofibrillar degeneration. O-GlcNacylation is a form not only of cytoplasmic but...
also of nuclear glycosylation and is present on RNA polymerase II and its associated transcriptional factors, nucleoporins etc[77] and could probably influence signal transduction.[78] Defective nuclear glycosylation may alter nuclear function which results in various defects in protein metabolism inducing amyloid deposition and protein misfolding.[55]

Welander Distal Myopathy (late onset, Type 1)

Welander described 249 patients from 72 pedigrees with autosomal dominant inheritance exclusively among the Swedish population.[79,80] Onset is late, usually after the age of 40 years, and muscle weakness initially involves the distal extensor muscles of the hands and feet, and later the arms and legs. Symptoms are slowly progressive but can be detected earlier in young middle-aged relatives of the patients.[79,81] Serum CK levels are normal or mildly elevated. On linkage analysis, Welander distal myopathy (WDM) was clearly separated from other distal myopathies and the gene was mapped to Chromosome 2p13,[82] but specific causative gene still awaits identification up to this time.

Pathological features in WDM include both myopathic and neuropathic changes, with RVs as the most striking finding.[83,84] On electron microscopy, there is focal myofibrillar degeneration, autophagic vacuoles and nuclear inclusions with tubulofilamentous structure measuring 15-20 nm in diameter,[79] similar to those seen in DMRV/hIBM. RVs are abundant in muscle biopsies from patients with moderate to severe symptoms, but are absent in the early stages of the disease. It is therefore still uncertain whether RV formation is a primary pathologic event that induces muscle fiber atrophy and loss, or is a secondary change associated with the primary dystrophic process.[83] Decreased numbers of myelinated fibers were found in some sural nerve biopsies, suggesting that there is also peripheral nerve involvement.[84]

Vocal cord and Pharyngeal weakness with Autosomal Dominant Distal Myopathy (MPD2)

A unique distal myopathy with vocal cord and pharyngeal weakness inherited as an autosomal dominant trait has been reported in a Caucasian family from Southern Tennessee.[85] The gene has been mapped Chromosome 5q31. The onset of the disease ranged from
35 to 57 years, averaging 45.7 years. Muscle weakness usually involves the feet and ankles, often in a peroneal distribution, and the hands. Vocal cord and pharyngeal weakness can be present at the onset of the distal extremity weakness. Serum CK levels are normal to mildly elevated. Muscle biopsies in six patients showed a noninflammatory myopathy with RVs, and groups of atrophic fibers consistent with denervation. No nuclear inclusions were found.

**Oculopharyngodistal Myopathy**

There are two categories of this disorder with different modes of inheritance, autosomal dominant[86,87] and recessive.[88] Four families with autosomal dominant inheritance who were first described by Satoyoshi et al.,[86] had late onset external ophthalmoplegia, facial and bulbar muscle weakness, and distally dominant limb muscle weakness. Leg muscle weakness usually precedes ocular and pharyngeal symptoms. The disease is slowly progressive. It remains to be determined whether oculopharyngodistal myopathy is a variant form of oculopharyngeal muscular dystrophy, because distal weakness has also been described in some oculopharyngeal muscular dystrophy families. Recently, we examined five patients with the clinical characteristics of oculopharyngodistal myopathy for GCG expansion in poly(A)-binding protein nuclear 1 gene, the causative gene defect for oculopharyngeal muscular dystrophy. Since only one of our five patients had the significant GCG expansion, oculopharyngodistal myopathy is concluded to be a genetically heterogeneous disorder.[89]

Oculopharyngodistal myopathy with an autosomal recessive inheritance has been reported in two patients from a Japanese family who had anterior tibial muscle weakness beginning after the age of 40 and 50 years respectively.[88] Distal upper extremity weakness and dropping eyes gradually became evident. In their muscle biopsies, there were myopathic changes with RVs in atrophic fibers and cytoplasmic filaments measuring 16-18 nm in diameter.

**Conclusion**

Precise diagnosis in distal myopathies remains as a challenge to clinicians, but some clues from the clinical history could be used for differential diagnosis [Figure 6]. The classification of distal myopathies would need some clarifications in the near future, especially that the molecular bases for such diseases are just starting to be clarified. More importantly, further analyses of the biological and molecular aspects of this disease in correlation to the clinical data, which are ongoing for some of the established entities, is expected to provide clues for understanding the mechanism behind why distal muscles are affected.

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