A group of muscle diseases, the distal myopathies, are notable for their preferential distal distribution of muscle weakness in contrast to most muscle conditions associated with proximal weakness. The major distal myopathies are summarized in Table 462e-9.

Clinical Features *Welander's*, *Udd's*, and *Markesbery-Griggs type distal myopathies* are all late-onset, dominantly inherited disorders of distal limb muscles, usually beginning after age 40 years. Welander's distal myopathy preferentially involves the wrist and finger extensors, whereas the others are associated with anterior tibial weakness leading to progressive footdrop. *Laing's distal myopathy* is also a dominantly inherited disorder heralded by tibial weakness; however, it is distinguished by onset in childhood or early adult life. *Nonaka's distal myopathy* and *Miyoshi's myopathy* are distinguished by autosomal recessive inheritance and onset in the late teens or twenties. Nonaka's and Williams' myopathy entails anterior tibial weakness, whereas Miyoshi's myopathy is unique in that gastrocnemius muscles are preferentially affected at onset. Finally, the *myofibrillar myopathies* (MFMs) are a clinically and genetically heterogeneous group of disorders that can be associated with prominent distal weakness; they can be inherited in an autosomal dominant or recessive pattern. Of note, Markesbery-Griggs myopathy (caused by mutations in ZASP) and LGMD1B (caused by mutations in myotilin) are in fact subtypes of myofibrillar myopathy.

Laboratory Features Serum CK level is particularly helpful in diagnosing Miyoshi's myopathy because it is very elevated. In the other conditions, serum CK is only slightly increased. EMGs are myopathic. In the MFMs, myotonic or pseudomyotonic discharges are common. Muscle biopsy shows nonspecific dystrophic features and, with the exception of Laing's and Miyoshi's myopathies, often shows rimmed vacuoles. MFM is associated with the accumulation of dense inclusions, as well as amorphous material best seen on Gomori trichrome and myofibrillar disruption on electron microscopy. Immune staining sometimes demonstrates accumulation of desmin and other proteins in MFM, large deposits of myosin heavy chain in the subsarcolemmal region of type 1 muscle fibers in Laing's myopathy, and reduced or absent dysferlin in Miyoshi's myopathy.

The affected genes and their gene products are listed in Table 462e-9.

TREATMENT DISTAL MYOPATHIES

Occupational therapy is offered for loss of hand function; ankle-foot orthoses can support distal lower limb muscles. The MFMs can be associated with cardiomyopathy (congestive heart failure or arrhythmias) and respiratory failure that may require medical management. Laing's-type distal myopathy can also be associated with a cardiomyopathy.

CONGENITAL MYOPATHIES

These rare disorders are distinguished from muscular dystrophies by the presence of specific histochemical and structural abnormalities in muscle. Although primarily disorders of infancy or childhood, three forms that may present in adulthood are described here: central core disease, nemaline (rod) myopathy, and centronuclear (myotubular) myopathy. Sarcotubular myopathy is caused by mutations in *TRIM-32* and is identical to LGMD2H. Other types, such as minicore myopathy (multi-minicore disease), fingerprint body myopathy, and cap myopathy, are not discussed.

CENTRAL CORE DISEASE

Patients with central core disease may have decreased fetal movements and breech presentation. Hypotonia and delay in motor milestones, particularly in walking, are common. Later in childhood, patients develop problems with stair climbing, running, and getting up from the floor. On examination, there is mild facial, neck-flexor, and proximal-extremity muscle weakness. Legs are more affected than arms. Skeletal abnormalities include congenital hip dislocation, scoliosis, and pes cavus; clubbed feet also occur. Most cases are nonprogressive, but exceptions are well documented. Susceptibility to malignant hyperthermia must be considered as a potential risk factor for patients with central core disease. Recent series have demonstrated that many cases of late-onset axial myopathy in which patients manifest with bent spine (camptocormia) or neck extensor weakness (neck extensor myopathy) are caused by mutations in the ryanodine receptor gene (*RYR1*). This illustrates the interesting spectrum of *RYR1* mutations.

The serum CK level is usually normal. Needle EMG demonstrates a myopathic pattern. Muscle biopsy shows fibers with single or multiple central or eccentric discrete zones (*cores*) devoid of oxidative enzymes. Cores occur preferentially in type 1 fibers and represent poorly aligned sarcomeres associated with Z disk streaming.

Autosomal dominant inheritance is characteristic; sporadic cases also occur. As alluded above, this myopathy is caused by point mutations of *RYR1*, encoding the calcium-release channel of the sarcoplasmic reticulum of skeletal muscle; mutations of this gene also account for some cases of inherited malignant hyperthermia (Chap. 23). Malignant hyperthermia is an allelic condition; C-terminal mutations of the *RYR1* gene predispose to this complication.

Specific treatment is not required, but establishing a diagnosis of central core disease is extremely important because these patients have a known predisposition to malignant hyperthermia during anesthesia.

NEMALINE MYOPATHY

The term *nemaline* refers to the distinctive presence in muscle fibers of rods or threadlike structures (Greek *nema*, "thread"). Nemaline myopathy is clinically heterogeneous. A severe neonatal form presents with hypotonia and feeding and respiratory difficulties, leading to early death. Nemaline myopathy usually presents in infancy or childhood with delayed motor milestones. The course is nonprogressive or slowly progressive. The physical appearance is striking because of the long, narrow facies, high-arched palate, and open-mouthed appearance due to a prognathous jaw. Other skeletal abnormalities include pectus excavatum, kyphoscoliosis, pes cavus, and clubfoot deformities. Facial and generalized muscle weakness, including respiratory muscle weakness, is common. An adult-onset disorder with progressive proximal or distal weakness may be seen. Myocardial involvement is occasionally present in both the childhood and adult-onset forms. The serum CK level is usually normal or slightly elevated. The EMG demonstrates a myopathic pattern. Muscle biopsy shows clusters of small rods (nemaline bodies), which occur preferentially, but not exclusively, in the sarcoplasm of type 1 muscle fibers. Occasionally, the rods are also apparent in myonuclei. The muscle often shows type 1 muscle fiber predominance. Rods originate from the Z disk material of the muscle fiber.

Six genes have been associated with nemaline myopathy. Five of these code for thin filament–associated proteins, suggesting disturbed assembly or interplay of these structures as a pivotal mechanism. Mutations of the nebulin (*NEB*) gene account for most cases, including both severe neonatal and early childhood forms, inherited as autosomal recessive disorders. Neonatal and childhood cases, inherited as predominantly autosomal dominant disorders, are caused by mutations of the skeletal muscle a-actinin (*ACTA1*) gene. In milder forms of the disease with autosomal dominant inheritance, mutations have been identified in both the slow a-tropomyosin (*TPM3*) and β;-tropomyosin (*TPM2*) genes accounting for <3% of cases. Muscle troponin T (*TNNT1*) gene mutations appear to be limited to the Amish population in North America. Mutations may also be seen in *NEM6* that encodes a putative BTB/Kelch protein. No specific treatment is available.

CENTRONUCLEAR (MYOTUBULAR) MYOPATHY

Three distinct variants of centronuclear myopathy occur. A neonatal form, also known as *myotubular myopathy*, presents with severe hypotonia and weakness at birth. The late infancy–early childhood form presents with delayed motor milestones. Later, difficulty with running and stair climbing becomes apparent. A marfanoid, slender body habitus, long narrow face, and high-arched palate are typical. Scoliosis and