filaments, producing profound weakness that can complicate the clinical course (e.g., by interfering with the weaning of a patient from a mechanical respirator).

Thyroid dysfunction can lead to several types of myopathy. *Thyrotoxic myopathy* presents most commonly as an acute or chronic proximal muscle weakness that may precede other signs of hyperthyroidism. Such patients may also present with *exophthalmic ophthalmoplegia*, characterized by swelling of the eyelids, edema of the conjunctiva, and diplopia. *Hypothyroidism* can cause cramping or aching of muscles, and decreased movement. Reflexes may be slowed. Findings in skeletal muscle include fiber atrophy, an increased number of abnormally localized nuclei, glycogen aggregates, and (occasionally) deposition of mucopolysaccharides in connective tissue.

Alcohol can also be myopathic. Most notably, binge drinking may produce an acute toxic syndrome of rhabdomyolysis, myoglobinuria, and renal failure. The affected individual may complain of acute myalgias that are generalized or confined to a single muscle group.

Inherited Diseases of Skeletal Muscle

Inherited mutations are responsible for a diverse collection of disorders marked by defects in skeletal muscle. In some of these disorders, skeletal muscle is the main site of disease, but in others multiple organs are involved. Of the other organs involved, the heart is of particular importance, since cardiac involvement is common and often life-limiting.

Historically, inherited myopathies have been subdivided into several broad categories based on inheritance pattern, anatomic pattern of muscle involvement, onset age, clinical course, and underlying pathogenesis.

Congenital myopathies (Table 27-2) typically present in infancy with muscle defects that tend to be static or to even improve over time. They are often associated with distinct structural abnormalities of the muscle.

Muscular dystrophies are characterized by progressive muscle damage that typically comes to attention after infancy. Exceptions to this rule are the *congenital muscular dystrophies*; these tend to present in infancy and are often associated with developmental abnormalities of the CNS as well as progressive muscle damage. These include two important groups:

- *Conditions with defects in extracellular matrix surrounding myofibers.* These are exemplified by Ullrich congenital musclar dystrophy (UCMD) and merosin deficiency. In the former the causative mutations involve one of three collagen VI alpha genes; in the case of merosin deficiency, the gene encoding merosin is disrupted. UCMD is characterized by hypotonia, proximal contractures and distal hyperextensibility. A morphologic hallmark is mismatched expression of normally co-localized matrix proteins perlecan and collagen VI.

Table 27-2 Congenital myopathies

Disease and Inheritance	Gene and Locus	Clinical Findings	Pathologic Findings
Central-core disease; autosomal dominant	Ryanodine receptor-1 (*RYR1*) gene; 19q13.1	Early-onset hypotonia and weakness; "floppy infant"; associated skeletal abnormalities like scoliosis, hip dislocation, or foot deformities; some RYR1 mutations cause central core disease, some malignant hyperthermia, and some both	Cytoplasmic cores represent demarcated central zones in which the normal arrangement of sarcomeres is disrupted and mitochondria are decreased in number
Nemaline myopathy (NEM)	AD NEM1—α-tropomyosin 3 (*TPM3*) gene; 1q22–q23 AR NEM2—nebulin (*NEB*) gene; 2q22 AR NEM3—α-actin-1 (*ACTA*) gene; 1q42 AR NEM4—tropomyosin-2 (*TPM2*) gene; 19p13.2–p13.1 AR NEM5—troponin T1 (*TNNT1*) gene; 19q13.4 AR NEM7—coffilin-2 (*CFL2*) gene; 14q12	Childhood weakness; some with more severe weakness, hypotonia at birth ("floppy infant")	Aggregates of spindle-shaped particles *(nemaline rods)*; occur predominantly in type 1 fibers; derived from Z-band material (α-actinin) and best seen on modified Gomori stain or by electron microscopy
Centronuclear myopathy	XL—myotubularin (*MTM1*) gene; Xq28 AD—dynamin-2 (and others) *DNM2* gene; 19p13.2 AR—amphiphysin-2(*BIN1*) gene; 2q14)	Severe congenital hypotonia, "floppy infant" and poor prognosis in X-linked form ("myotubular myopathy") Childhood onset or young adult onset with other variants with weakness and hypotonia	Many fibers contain nuclei in the geometric center of the myofiber; central nuclei are more common in type 1 fibers, which are small in diameter, but can occur in both fiber types
Congenital fiber type disproportion	Selenoprotein 1 *(SEPN1)* gene; 1p36.11 Alpha-actin-1 *(ACTA1)* gene; 1q42.13 Tropomyosin 3 *(TPM3)* gene; 1q21.3	Hypotonia, weakness, failure to thrive, facial and resp. weakness, contractures Wide phenotypic spectrum Mutations in SEPN1 are also associated with protein aggregate myopathy and rigid spine muscular dystrophy; mutations in ACTA1 are also associated with nemaline myopathy and protein aggregate myopathy; mutations in TPM3 are also associated with nemaline myopathy	Predominance and atrophy of type I fibers (not specific)

AD, Autosomal dominant; AR, autosomal recessive; XL, X-linked.