TABLE 462e-6 AUTOSOMAL DOMINANT LIMB-GIRDLE MUSCULAR DYSTROPHIES (LGMDs)

Disease	Clinical Features	Laboratory Features	Abnormal Protein
LGMD1A	Onset second to eighth decade	Serum CK 2× normal	Myotilin
	Muscle weakness affects proximal and distal limb muscles, vocal cords, and pharyngeal muscles	EMG myopathic and may have pseudomotonic discharges	
		Muscle biopsy: features of MFM	
LGMD1B	Onset first or second decade	Serum CK 3–5× normal	Lamin A/C
	Proximal lower limb weakness and cardiomyopathy with conduction defects	EMG myopathic	
	Some cases indistinguishable from Emery-Dreifuss muscular dystrophy with joint contractures		
LGMD1C	Onset in early childhood	Serum CK 4–25× normal	Caveolin-3
	Proximal weakness	EMG myopathic	
	Gowers' sign, calf hypertrophy, rippling muscles		
	Exercise-related muscle cramps		
LGMD1D	Onset second to sixth decade	Serum CK 2–3× normal	DNAJB6
	Proximal and distal muscle weakness	EMG myopathic	
		Muscle biopsy: features of MFM	
LGMD1E	Onset first to sixth decade	Serum CK 2–4× normal	Desmin
	Proximal or distal muscle weakness	EMG myopathic and may have pseudomotonic discharges	
	Cardiomyopathy and arrhythmias	Muscle biopsy: features of MFM	
LGMD1F	Onset infancy to sixth decade	Serum CK normal to 20× normal	TNPO3
	Proximal or distal weakness	EMG myopathic	
	May have early contractures resembling Emery-Dreifuss syndrome	Muscle biopsy may show enlarged nuclei with central pallor, rimmed vacuoles, and filamentous inclusions	

Abbreviations: CK, creatine kinase; EMG, electromyography; MFM, myofibrillar myopathy; NCS, nerve conduction studies.

playing. Running, jumping, and hopping are invariably abnormal. By age 5 years, muscle weakness is obvious by muscle testing. On getting up from the floor, the patient uses his hands to climb up himself (Gowers' maneuver [Fig. 462e-4]). Contractures of the heel cords and iliotibial bands become apparent by age 6 years, when toe walking is associated with a lordotic posture. Loss of muscle strength is progressive, with predilection for proximal limb muscles and the neck flexors; leg involvement is more severe than arm involvement. Between ages 8 and 10 years, walking may require the use of braces; joint contractures and limitations of hip flexion, knee, elbow, and wrist extension are made worse by prolonged sitting. Prior to the use of glucocorticoids, most boys became wheelchair dependent by 12 years of age. Contractures become fixed, and a progressive scoliosis often develops that may be associated with pain. The chest deformity with scoliosis impairs pulmonary function, which is already diminished by muscle weakness. By age 16–18 years, patients are predisposed to serious, sometimes fatal pulmonary infections. Other causes of death include aspiration of food and acute gastric dilation.

A cardiac cause of death is uncommon despite the presence of a cardiomyopathy in almost all patients. Congestive heart failure seldom occurs except with severe stress such as pneumonia. Cardiac arrhythmias are rare. The typical electrocardiogram (ECG) shows an increased net RS in lead V_1; deep, narrow Q waves in the precordial leads; and tall right precordial R waves in V_1. Intellectual impairment in Duchenne dystrophy is common; the average intelligence quotient (IQ) is ~1 standard deviation (SD) below the mean. Impairment of intellectual function appears to be nonprogressive and affects verbal ability more than performance.

Laboratory Features Serum CK levels are invariably elevated to between 20 and 100 times normal. The levels are abnormal at birth but decline late in the disease because of inactivity and loss of muscle mass. EMG demonstrates features typical of myopathy. The muscle biopsy shows muscle fibers of varying size as well as small groups of necrotic and regenerating fibers. Connective tissue and fat replace lost muscle fibers. A definitive diagnosis of Duchenne dystrophy can be established on the basis of dystrophin deficiency in a biopsy of muscle tissue or mutation analysis on peripheral blood leukocytes, as discussed below.

Duchenne dystrophy is caused by a mutation of the gene that encodes dystrophin, a 427-kDa protein localized to the inner surface of the sarcolemma of the muscle fiber. The dystrophin gene is >2000 kb in size and thus is one of the largest identified human genes. It is localized to the short arm of the X chromosome at Xp21. The most common gene mutation is a deletion. The size varies but does not correlate with disease severity. Deletions are not uniformly distributed over the gene but rather are most common near the beginning (5′ end) and middle of the gene. Less often, Duchenne dystrophy is caused by a gene duplication or point mutation. Identification of a specific mutation allows for an unequivocal diagnosis, makes possible accurate testing of potential carriers, and is useful for prenatal diagnosis.

A diagnosis of Duchenne dystrophy can also be made by Western blot analysis of muscle biopsy specimens, revealing abnormalities on the quantity and molecular weight of dystrophin protein. In addition, immunocytochemical staining of muscle with dystrophin antibodies can be used to demonstrate absence or deficiency of dystrophin localizing to the sarcolemmal membrane. Carriers of the disease may demonstrate a mosaic pattern, but dystrophin analysis of muscle biopsy specimens for carrier detection is not reliable.

Pathogenesis Dystrophin is part of a large complex of sarcolemmal proteins and glycoproteins (Fig. 462e-6). Dystrophin binds to F-actin at its amino terminus and to β-dystroglycan at the carboxyl terminus. β-Dystroglycan complexes to α-dystroglycan, which binds to laminin in the extracellular matrix (ECM). Laminin has a heterotrimeric molecular structure arranged in the shape of a cross with one heavy chain and two light chains, β_1 and γ_1. The laminin heavy chain of skeletal muscle is designated laminin α_2. Collagen proteins IV and VI are also found in the ECM. Like β-dystroglycan, the transmembrane sarcoglycan proteins also bind to dystrophin; these five proteins (designated α- through ε-sarcoglycan) complex tightly with each other. More recently, other membrane proteins implicated in muscular dystrophy have been found to be loosely affiliated with constituents of the dystrophin complex. These include caveolin-3, α_7 integrin, and collagen VI.