myasthenia, the mother herself has autoimmune myasthenia that is transmitted passively to the newborn via the immune system. In congenital myasthenia, the infant has an inherited defect in some component of the neuromuscular junction, rather than an autoimmune disease, and thus does not have serum antibodies to the nicotinic ACh receptor or MuSK.

Congenital myasthenic syndromes fall into three broad groups based on the site of the defect in the neuromuscular synapse: presynaptic, synaptic cleft, and postsynaptic forms. Clinical features common to all three types include a positive family history, weakness with easy fatigability (present since infancy), drooping of the eyelids (ptosis), a decremental response to repetitive stimulation on EMG, and negative screening for anti-nicotinic ACh receptor antibodies. Subnormal development of the skeletal muscles reflects the fact that normal function at the neuromuscular synapse is required to maintain normal muscle bulk.

In one presynaptic form of congenital myasthenia, the enzyme choline acetyltransferase is absent or reduced in the distal motor terminal. This enzyme is essential for the synthesis of ACh from choline and acetyl-CoA (Chapter 16). In its absence, the synthesis of ACh is impaired. The result is weakness that usually begins in infancy or early childhood. In another presynaptic form of congenital myasthenia, the number of quanta of ACh released after an action potential is less than normal; the molecular basis for this defect is not known.

Congenital myasthenia may also result from the absence of acetylcholinesterase in the synaptic cleft. In this circumstance, end-plate potentials and miniature end-plate potentials are not small, as in autoimmune myasthenia, but are markedly prolonged, which may explain the repetitive response of the evoked muscle potential in those patients. Cytochemical studies indicate that ACh-esterase is absent from the basement membranes. At the same time, nicotinic ACh receptors are preserved.

The physiological consequence of ACh-esterase deficiency is sustained action of ACh on the end-plate and ultimately the development of an end-plate myopathy. This myopathy indicates that skeletal muscle can react adversely to excessive stimulation at the neuromuscular junction. In treating this disorder, it is critical to avoid using agents that inhibit ACh-esterase, which can increase the electrical firing at the end-plate and thereby exacerbate the muscle weakness.

The majority of congenital myasthenia cases are caused by primary mutations in the genes encoding different subunits of the ACh receptor. The *slow channel syndrome* is characterized by prominent limb weakness but little weakness of cranial muscles (the reverse of the pattern usually seen in autoimmune myasthenia, where muscles of the eyes and oropharynx are almost always affected). End-plate currents are slow to decay, and there is abnormal prolongation of channel opening. The mutations probably act both by increasing the affinity of the nicotinic ACh receptor for ACh, thereby prolonging the effects of this transmitter, and by directly slowing the channel closing rate. In some instances, quinidine is effective therapy for slow channel syndrome because it blocks the open receptor-channel. As with ACh-esterase mutations, end-plate function degenerates due to excessive postsynaptic stimulation, so anticholinesterase medications are potentially dangerous.

In the fast channel syndrome, a different set of mutations in one or more nicotinic ACh receptor subunits leads to an accelerated rate of channel closing and end-plate current decay. The fast channel syndrome may respond to either acetylcholinesterase inhibitors or 3,4-diaminopyridine. The latter blocks a presynaptic potassium conductance and thereby increases the probability of quantal release of ACh, probably by prolonging the action potential.

Lambert-Eaton Syndrome and Botulism Also Alter Neuromuscular Transmission

Some patients with cancer, especially small-cell cancer of the lung, have a syndrome of proximal limb weakness and a neuromuscular disorder with characteristics that are the opposite of those seen in myasthenia gravis. Instead of a decline in synaptic response to repetitive nerve stimulation, the amplitude of the evoked potential increases; that is, neuromuscular transmission is facilitated. Here, the first postsynaptic potential is abnormally small, but subsequent responses increase in amplitude so that the final summated potential is two to four times the amplitude of the first potential.

This disorder, *Lambert-Eaton syndrome*, is attributed to the action of antibodies against voltage-gated Ca^{2+} channels in the presynaptic terminals. It is thought that these antibodies react with the channels, degrading the channels as the antibody–antigen complex is internalized. Calcium channels similar to those of presynaptic terminals are found in cultured cells from the small-cell carcinoma of the lung; development of antibodies against these antigens in the tumor might be followed by pathogenic action against nerve terminals, another kind of molecular mimicry.

A facilitating neuromuscular block is also found in human botulism, as the botulinum toxin also impairs release of ACh from nerve terminals. Both botulism

and Lambert-Eaton syndrome are ameliorated by administration of calcium gluconate or guanidine, agents that promote the release of ACh. These drugs are less effective than immunosuppressive treatments for long-term control of Lambert-Eaton syndrome, which is chronic. Botulism, on the other hand, is transient, and if the patient is kept alive during the acute phase by treating symptoms, the disorder disappears in weeks as the infection is controlled and botulinum is inactivated.

Diseases of Skeletal Muscle Can Be Inherited or Acquired

The weakness seen in any myopathy is usually attributed to degeneration of muscle fibers. At first, the missing fibers are replaced by regeneration of new fibers. Ultimately, however, renewal cannot keep pace and fibers are progressively lost. This leads to the appearance of compound motor unit potentials of brief duration and reduced amplitude. The decreased number of functioning muscle fibers then accounts for the diminished strength, whether the skeletal muscle disease is inherited or acquired.

Dermatomyositis Exemplifies Acquired Myopathy

The prototype of an acquired myopathy is dermatomyositis, defined by two clinical features: rash and myopathy. The rash has a predilection for the face, chest, and extensor surfaces of joints, including the fingers. The myopathic weakness primarily affects proximal limb muscles. The rash and weakness usually appear simultaneously and become worse in a matter of weeks. The weakness may be mild or life-threatening.

This disorder affects children or adults. About 10% of adult patients have malignant tumors. Although the pathogenesis is not known, dermatomyositis is thought to be an autoimmune disorder of small intramuscular blood vessels.

Muscular Dystrophies Are the Most Common Inherited Myopathies

The best-known inherited muscle diseases are the muscular dystrophies; several major types are distinguished by clinical and genetic patterns (Table 57–4). Some types are characterized by weakness alone (Duchenne, facioscapulohumeral, and limb-girdle dystrophies); others (eg, the myotonic muscular dystrophies) have additional clinical features. Most are recessively inherited and begin in early childhood (Duchenne, Becker, and limb-girdle dystrophy); less frequently, the dystrophies are dominantly inherited (facioscapulohumeral or myotonic dystrophy). The cardinal trait of limb-girdle dystrophies is slowly progressive proximal weakness; in the myotonic muscular dystrophies, progressive weakness is accompanied by severe muscle stiffness.

Duchenne muscular dystrophy affects only males because it is transmitted as an X-linked recessive trait. It starts in early childhood and progresses relatively rapidly, so that patients are in wheelchairs by age 12 and usually die in their third decade. This dystrophy is caused by mutations that severely reduce levels of dystrophin, a skeletal muscle protein that apparently confers tensile strength to the muscle cell. In a related inherited muscle disorder, Becker muscular dystrophy, dystrophin is present but is either abnormal in size or reduced in quantity. Becker dystrophy is thus typically much milder, although there is considerable clinical variability according to how much dystrophin is retained; individuals with Becker dystrophy typically are able to walk well into adulthood, albeit with weakness of the proximal leg and arm muscles.

Dystrophin is encoded by the *DMD* gene, the second largest human gene, spanning about 2.5 million base pairs, or 1% of the X chromosome and 0.1% of the total human genome (Figure 57–10A). It contains at least 79 exons that encode a 14-kb mRNA. The inferred amino acid sequence of the dystrophin protein suggests a rod-like structure and a molecular weight of 427,000, with domains similar to those of two cytoskeletal proteins, alpha-actinin and spectrin. Dystrophin is localized to the inner surface of the plasma membrane. The amino terminus of dystrophin is linked to cytoskeletal actin, whereas the carboxy terminus is linked to the extracellular matrix by transmembrane proteins (Figure 57–11).

The majority of boys with Duchenne muscular dystrophy have a deletion in the *DMD* gene; about a third have point mutations. In either case, these mutations introduce premature stop codons in the mutant RNA transcripts that prevent synthesis of full-length dystrophin. Becker dystrophy is also caused by deletions and missense mutations, but the mutations do not introduce stop codons. The resulting dystrophin protein is nearly normal in length and can at least partially substitute for normal dystrophin (Figure 57–10B). Some boys with Duchenne dystrophy benefit from treatment with ASOs that cause skipping of specific mutant exons, generating a shortened but partially functional dystrophin protein (Figure 57–10C). Another promising approach is to deliver a form of the *DMD* gene to the muscle using adeno-associated virus. While the full-length *DMD* gene is too large to fit

Table 57–4 Representative Muscular Dystrophy Genes

Site of primary defect	Protein	Disease
Extracellular matrix	Collagen VI α1, α2, and α3	Bethlem myopathy
	Merosin laminin α2-subunit	Congenital myopathy
Transmembrane	α-Sarcoglycan	LGMD-2D
	β-Sarcoglycan	LGMD-2E
	χ-Sarcoglycan	LGMD-2C
	σ-Sarcoglycan	LGMD-2F
	Dysferlin	LGMD-2B, Miyoshi myopathy
	Caveolin-3	LGMD-1C, rippling muscle disease
	α7-Integrin	Congenital myopathy
	XK protein	McLeod syndrome
Submembrane	Dystrophin	Duchenne, Becker dystrophies
Sarcomere/myofibrils	Tropomyosin B	Nemaline rod myopathy
	Calpain	LGMD-2A
	Titin	Distal (Udd) dystrophy
	Nebulin	Nemaline rod myopathy
	Telethonin	LGMD-2G
	Skeletal muscle actin	Nemaline rod myopathy
	Troponin	Nemaline rod myopathy
Cytoplasm	Desmin	Desmin storage myopathy
	αβ-Crystallin	Distal myofibrillar myopathy
	Selenoprotein	Rigid spine syndrome
	Plectin	Epidermolysis bullosa simplex
Sarcoplasmic reticulum	Ryanodine receptor	Central core disease, malignant hyperthermia
	SERCA1	Brody myopathy
Nucleus	Emerin	Emery-Dreifuss dystrophy
	Lamin A/C	Emery-Dreifuss dystrophy
	Poly A binding protein, repeat	Oculopharyngeal dystrophy
Enzymes/miscellaneous	Myotonin kinase, CTG repeat	Myotonic dystrophy
	Zinc finger 9, CCTG repeat	Proximal myotonic dystrophy
	Epimerase	Inclusion body myositis
	Myotubularin	Myotubular myopathy
	Chorein	Chorea-acanthocytosis
Golgi apparatus	Fukutin	Fukuyama congenital dystrophy
	Fukutin-related peptide	Limb-girdle dystrophy
	POMT1	Congenital muscular dystrophy
	POMGnT1	Congenital muscular dystrophy

LGMD, limb-girdle muscular dystrophy.

within that virus, there is evidence that some truncated versions of dystrophin retain partial function; indeed, severely shortened dystrophins have been discovered in patients with very mild forms of Becker dystrophy. Packaging of genes encoding mini-dystrophins into the adeno-associated virus is feasible, permitting delivery to skeletal muscle and improvement of the dystrophic process (Figure 57–10C).

The discovery of the affected gene product in Duchenne muscular dystrophy by Louis Kunkel in the mid-1980s stimulated rapid discovery of numerous other novel muscle proteins, some with an intimate relationship to dystrophin. As a result, the primary genetic and protein defects underlying most major muscular dystrophies have now been identified (Figure 57–11). From these, several themes have emerged in our understanding of the biology of the muscular dystrophies.

First, and perhaps most important, is the concept that normal muscle requires a functional unit linking the contractile proteins through dystrophin to a complex of dystrophin-associated transmembrane proteins (sarcoglycans, β-dystroglycan) that, in turn, are linked to proteins at the membrane surface (eg, α-dystroglycan) and the extracellular matrix (eg, laminin). Disruption of this linked network due to a mutation in one of the proteins leads to reductions in levels of many of the proteins (Table 57–4).

Second, some of these proteins have attached sugar groups that are critical for binding the extracellular matrix proteins. Genetic defects in several of the intracellular Golgi proteins (fukutin, fukutin-related peptide, POMT1, POMTGn1) impair the deposition of the sugars (glycosylation) of the transmembrane proteins, often leading to aberrant muscle development and pronounced clinical pathology, not only in muscle but sometimes in the brain.

Third, the integrity of the extracellular matrix is essential for normal muscle function: Defects in extracellular matrix proteins (laminin α2 or α7-integrin) also cause muscular dystrophies.

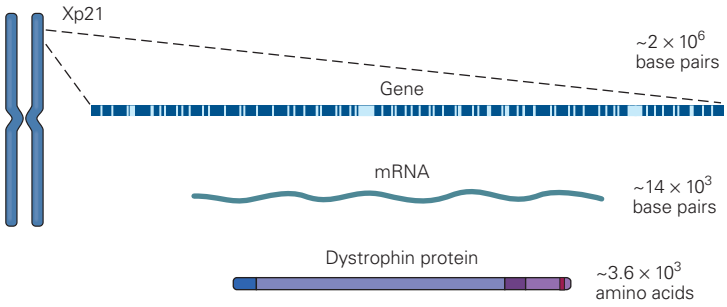
Fourth, other proteins (eg, dysferlin), distinct from those complexed with dystrophin, mediate membrane repair after injury. Whereas dystrophin is important in maintaining the tensile strength and integrity of the muscle membrane, dysferlin and its binding partner caveolin-3 are central to generating rafts of vesicles that coalesce and heal breaches that occur in the muscle membrane.

It is of clinical interest that disorders due to defects in many of these proteins are less aggressive and more slowly disabling than those in Duchenne dystrophy. Defects in this diverse group of skeletal muscle proteins lead to the limb-girdle phenotype, characterized by slowly progressive proximal weakness of the arms and legs. Most are recessively inherited; mutations in both copies of a particular gene prevent expression of the normal protein product and lead to loss of function of that protein. Some limb-girdle genes are dominantly transmitted; mutations in only one copy of the gene in a pair can cause pathology. As in most primary muscle diseases, in the limb-girdle phenotype, weakness is prominent in the torso and in proximal muscles of the arms and legs. Why this pattern is so common is not known, especially since the affected proteins are expressed in both distal and proximal muscles. The pattern of degeneration most likely reflects muscle use. The proximal muscles are, on average, more subject to low-level but chronic contractile activity because they serve as antigravity muscles.

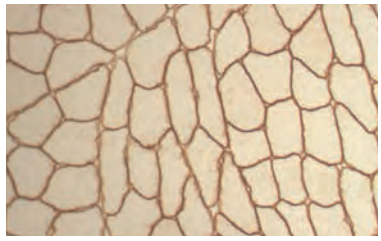
Myotonic dystrophy has several distinctive features including an autosomal inheritance pattern, weakness that is predominantly distal, involvement of nonmuscle tissues, and striking muscle stiffness (*myotonia*). The stiffness is induced by excessive electrical discharges of the muscle membrane associated with voluntary muscle contractions or percussion or electrical stimulation of the muscle. It is most intense within the first few movements after a period of rest and improves with continued muscular activity ("warm-up" phenomenon). Patients typically have difficulty relaxing the grip of a handshake for several seconds, opening the eyelids after forceful squinting, or moving their legs with the first few steps after rising from a chair. EMG demonstrates that the muscle cell membrane is electrically hyperexcitable in myotonic dystrophy; after a contraction, bursts of repetitive action potentials wax and wane in amplitude and frequency (20–100 Hz) over several seconds and thereby delay relaxation (Figure 57–12A). This sustained contraction is truly myogenic and independent of nerve supply because it persists after blockade of either the incoming motor nerve or neuromuscular transmission with agents such as curare.

The manifestations of myotonic dystrophy are not confined to muscles, however. Almost all patients have cataracts; affected men commonly have testicular atrophy and baldness and often develop cardiac conduction system defects that lead to irregularities in the heartbeat. The primary genetic defect is a dominantly transmitted expansion of a triplet of base pairs (CTG) in a noncoding region of a gene (myotonin kinase) on chromosome 19. RNA transcripts of the expanded CTG segments accumulate in the nucleus and alter splicing of several critical genes, including the ClC-1 Cl^- channel. Loss of function of this channel leads to

A The *DMD* gene

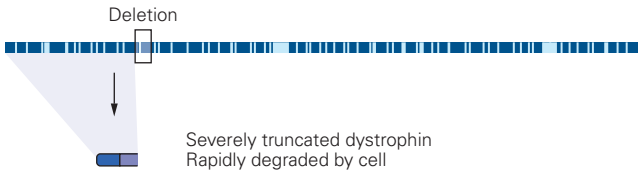


Normal dystrophin staining

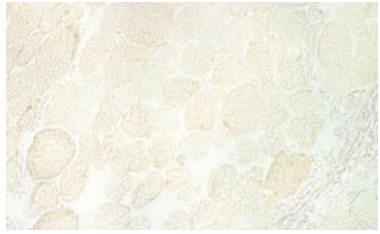


B Effects of deletion

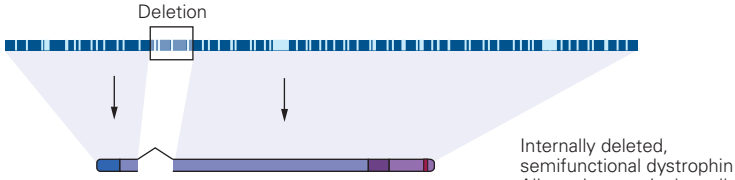
1 Deletion of single exon results in severe (Duchenne) dystrophy



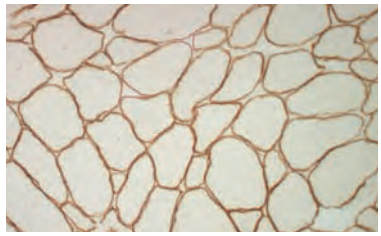
Dystrophin staining in Duchenne dystrophy



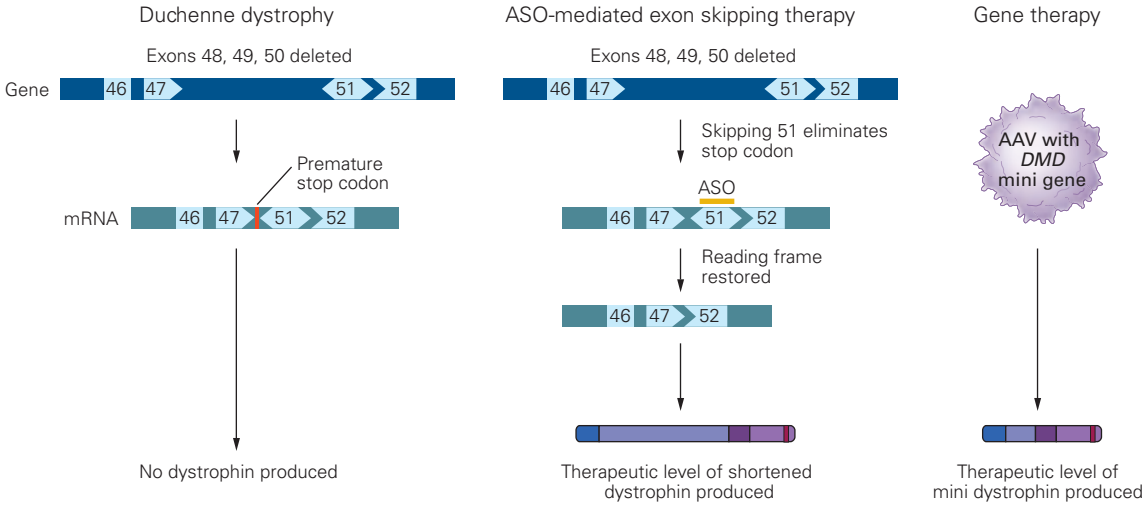
2 Deletion of four exons results in milder (Becker) dystrophy



Dystrophin staining in Becker dystrophy



C Exon skipping and mini gene replacement therapies in Duchenne dystrophy



excessive electrical activity in skeletal muscle and, as a consequence, myotonia. As discussed below, direct mutations in the same Cl^- channel gene can lead to a similar abnormal pattern of muscle activity.

Some Inherited Diseases of Skeletal Muscle Arise From Genetic Defects in Voltage-Gated Ion Channels

The electrical excitability of skeletal muscle is essential to the rapid and nearly synchronous contraction of an entire muscle fiber. The depolarizing end-plate potential at the neuromuscular junction triggers an action potential that propagates longitudinally along the surface of the muscle fiber and radially inward along the transverse tubules, invaginations of the fiber membrane in apposition with the sarcoplasmic reticulum (Chapter 31).

Depolarization of the transverse tubules induces a conformational change in L-type voltage-gated Ca^{2+} channels that is directly transmitted to Ca^{2+} release channels (the ryanodine receptors) in the sarcoplasmic reticulum, causing the channels to open. The release of Ca^{2+} from the sarcoplasmic reticulum raises myoplasmic Ca^{2+} and thus activates adenosine triphosphate (ATP)-dependent movement of actin-myosin filaments.

Normally, one action potential is generated in a muscle fiber for each end-plate potential. Repolarization of the muscle action potential depends on inactivation of Na^+ channels and the opening of delayed-rectifier voltage-gated K^+ channels similar to those in axons. This repolarization is also augmented by Cl^- influx through the ClC-1 Cl^- channels. Inherited muscle diseases arise from mutations in any one of these channels.

The electrical coupling of the end-plate potential to depolarization of the transverse tubules is disrupted in several inherited diseases of muscle. These disorders reflect a variety of defects in excitability, ranging from complete failure of action potential generation to prolonged bursts of repetitive discharges in response to a single stimulus (Figure 57–12). The derangements of muscle fiber excitability are transient and result in periodic paralysis from reduced excitability or myotonia from hyperexcitability. Between episodes, muscle function is normal. These are rare diseases of skeletal muscle, with a prevalence of 1 per 100,000 or less. Inheritance is autosomal dominant, except for one form of myotonia.

Weakness may be so severe during an attack of periodic paralysis that a patient is bedridden for hours, unable to raise an arm or leg off the bed. Fortunately, during such attacks, the muscles of respiration and swallowing are spared, so life-threatening respiratory arrest does not occur; consciousness and sensation are also spared. Attack frequency varies from almost daily to only a few in a lifetime.

During an attack, the resting potential of affected muscles is depolarized from a normal value of –90 mV

Figure 57–10 (Opposite) Two forms of muscular dystrophy are caused by deletion mutations in the dystrophin gene. (After Hoffman and Kunkel 1989.)

A. The relative position of the *DMD* gene within the Xp21 region of the X chromosome. An enlargement of this locus shows the 79 exons (**light blue lines**) and introns (**dark blue lines**) defining the gene with about 2.0×10^6 base pairs. Transcription of the gene gives rise to mRNA (about 14×10^3 base pairs), and translation of this mRNA gives rise to the protein dystrophin (molecular weight 427,000).

B. A deletion that disrupts the reading frame results in the clinically severe Duchenne muscular dystrophy, whereas a deletion that preserves the reading frame usually results in the clinically milder Becker muscular dystrophy. In both cases, the gene is transcribed into mRNA and the exons flanking the deletion are spliced together. 1. If the borders of neighboring exons do not maintain the translational reading frame, then incorrect amino acids are inserted into the growing polypeptide chain until an abnormal stop codon is reached, causing premature termination of the protein. The truncated protein may be unstable, may fail to be localized in the membrane, or may fail to bind to glycoproteins. Functional dystrophin is then almost totally absent. 2. If the deletion preserves the reading frame, a dystrophin molecule is produced with an internal deletion but intact ends. Although the protein is smaller than normal and may be present in less than normal amounts, it can often suffice to preserve some muscle function.

C. One approach to correcting a deletion of the *DMD* gene is to induce formation of an mRNA transcript that skips one or more exons to restore the reading frame. For example, when there is a deletion of exons 48, 49, and 50, the splicing of exon 47 to exon 51 yields a transcript that is out of frame, in which a stop codon is introduced, preventing production of dystrophin. However, addition of an antisense oligonucleotide (**ASO**) that binds exon 51 and prevents its splicing will promote the in-frame splicing of exon 47 to exon 52. Although this transcript is slightly shorter than normal, as is the resulting dystrophin protein, the protein will nonetheless function well enough to ameliorate the muscle degeneration. Another therapeutic approach is to deliver a short form of the dystrophin gene (mini- or micro-dystrophin, ~30% of the full-length protein) to the muscle using adeno-associated virus (**AAV**); full-length dystrophin is too large to be delivered within the AAV.

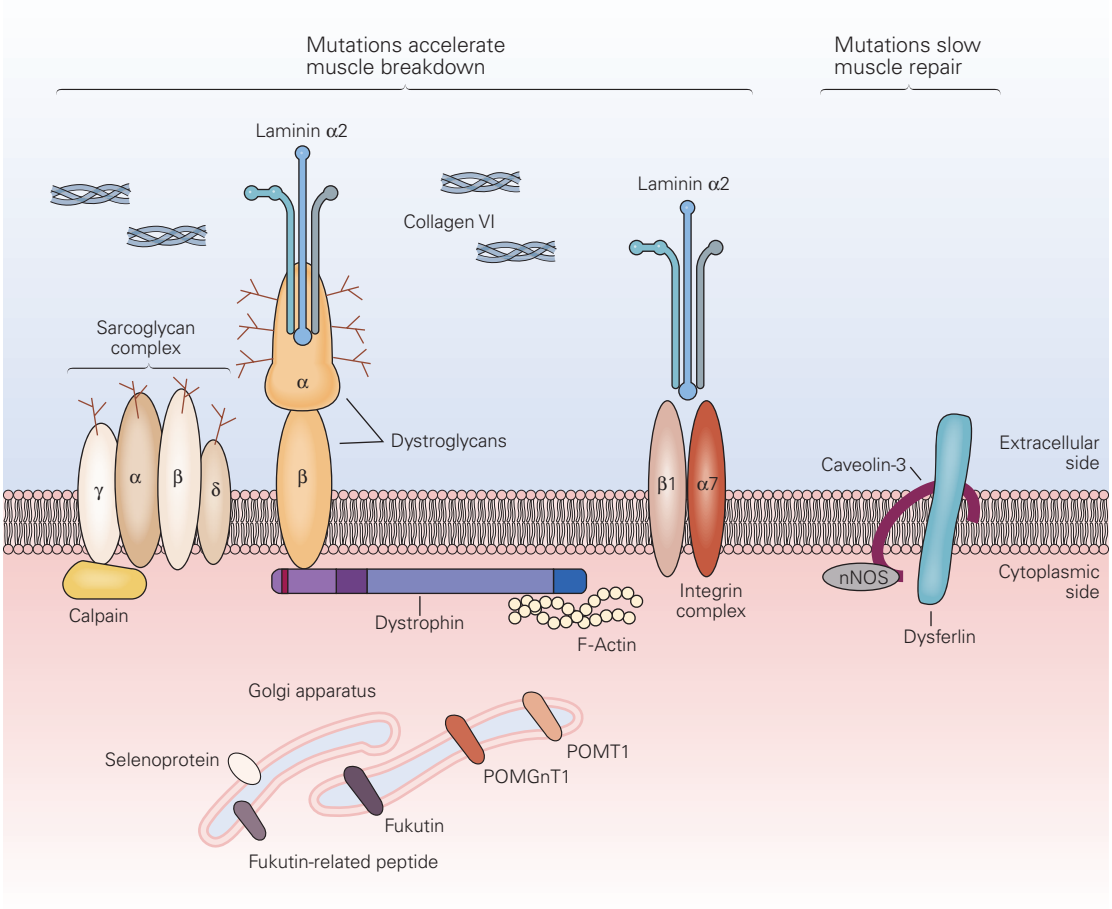


Figure 57–11 **In muscular dystrophy, mutated proteins either weaken the muscle cell membrane or slow its repair after injury.** For example, a deficiency of dystrophin, a submembrane protein, causes Duchenne muscular dystrophy. Dystrophin interacts with complexes of other membrane proteins that are mutated in other dystrophies, including the dystroglycans and the sarcoglycans, which are closely associated with extracellular proteins such as laminin α2 and collagen. Several other proteins mutated in different forms of muscular dystrophy are normally present in the Golgi apparatus, where they are essential for adding sugar groups to membrane proteins. These include **POMT1** (protein-O-mannosyl transferase 1), **POMGnT1** (protein-O-mannosyl α-,2-*N*-acetylglucosaminyl transferase), fukutin, fukutin-related peptide, and a selenoprotein. Dysferlin, which is mutated in still other dystrophies, is involved in the repair of skeletal muscle membrane after injury. (Adapted, with permission, from Brown and Mendell 2005.)

to about –60 mV. At this potential, most Na^+ channels are inactivated, rendering the muscle fiber chronically refractory and thus unable to generate action potentials. Recovery of strength occurs spontaneously and is associated with repolarization to a resting potential within a few millivolts of normal and recovery of excitability.

Two variants of periodic paralysis have been delineated. Hyperkalemic periodic paralysis attacks occur during periods of high venous K^+ (≥6.0 mM versus normal levels of 3.5–4.5 mM). Ingesting foods with high K^+ content such as bananas or fruit juice may trigger an attack. Conversely, hypokalemic periodic paralysis presents as episodic weakness in association with low blood K^+ (≤2.5 mM). Affected muscle is paradoxically depolarized in the setting of reduced extracellular K^+, which shifts the reversal potential for K^+ to more negative values. Both forms are inherited as autosomal dominant traits.

Hyperkalemic periodic paralysis is caused by missense mutations in a gene that encodes the pore-forming subunit of a voltage-gated Na^+ channel

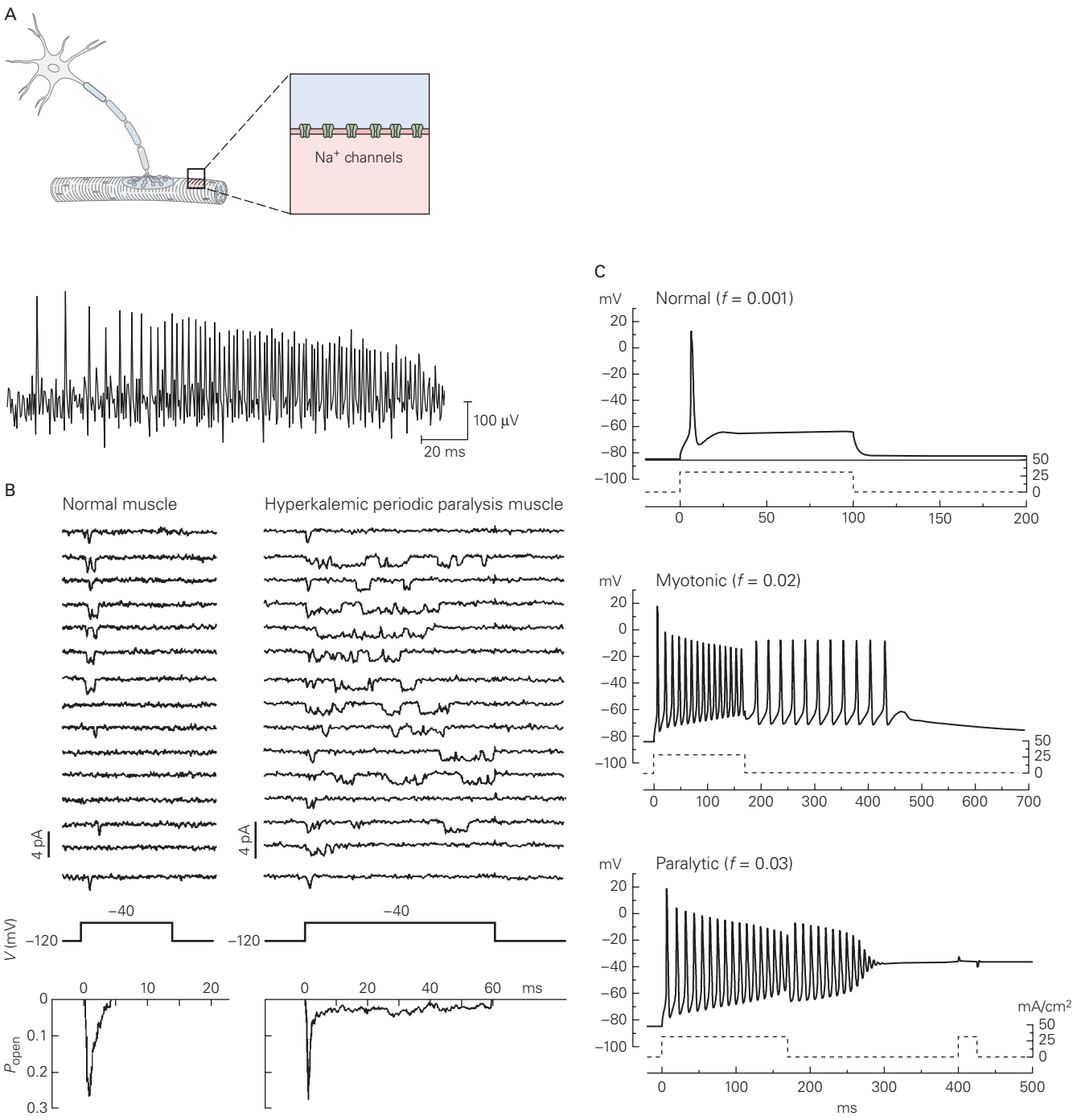


Figure 57–12 Myotonia or paralysis can result from genetically altered function in ion channels in skeletal muscle.

A. The electrical signature of myotonia (muscle stiffness) is a rapid burst of action potentials in response to a single stimulus. The action potentials, here shown in extracellular recordings, vary in amplitude and wax and wane in frequency. Such a burst may follow a voluntary muscle contraction or a mechanical stimulus, such as percussion of the muscle.

B. Cell-attached patch recordings from cultured human muscle cells. In normal muscle, the Na^+ channels open early and briefly in response to a 60 msec voltage-clamp depolarization from –120 mV to –40 mV. In muscle from patients with hyperkalemic periodic paralysis (defective M1592V Na^+ channel), the prolonged openings and reopenings indicate impaired inactivation. The probability of channel opening (obtained by averaging individual records) persists in the hyperkalemic muscle following inactivation. (Reproduced, with permission, from Cannon 1996.)

C. Even modest disruption of Na^+ channel inactivation is sufficient to produce bursts of myotonic discharges or depolarization-induced loss of excitability. These computer simulation records show muscle voltage in response to depolarizing current injection (**dashed line**). Among the total pool of mutant channels, a small fraction (*f*) fails to inactivate normally. In these simulations, *f* was varied from normal to values appropriate for myotonic or paralytic muscle. (Reproduced, with permission, from Cannon 1996.)

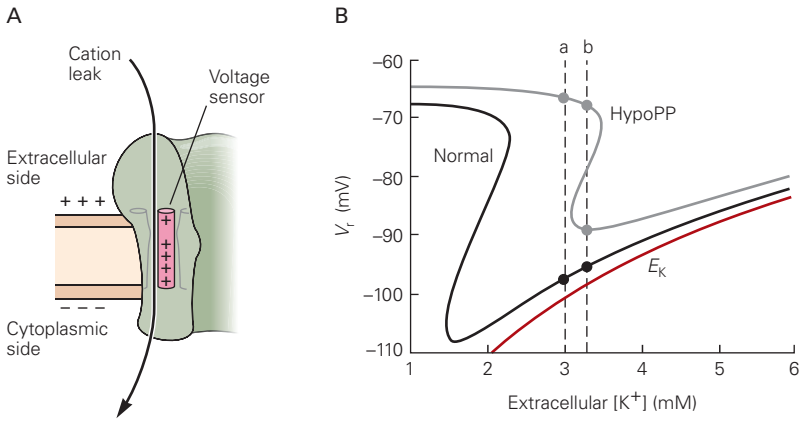


Figure 57–13 Hypokalemic periodic paralysis (HypoPP) is caused by leaky ion channels.

A. In HypoPP, missense mutations in the voltage-sensor domains create leaky Ca^{2+} or Na^+ channels that allow cation influx via an anomalous pathway separate from the channel pore.

B. Although this leak is small (~0.5% of the total resting membrane conductance), model simulations show that it causes an increased susceptibility to depolarization of resting potential (V_r), resulting in inexcitability and weakness as the external $[K^+]$ is lowered. This paradoxical depolarization of V_r diverges from the Nernst potential for K^+ (E_K) because of loss of the contribution from the inward rectifier K^+ channel in low $[K^+]$. Normally, this depolarization occurs only at extremely low $[K^+]$ (<2 mM) and is not seen in healthy people, but for patients with HypoPP, the cation leak shifts the depolarization point into the physiological range of $[K^+]$. For this simulation, in 3.3 mM $[K^+]$ (**line b**), excitability is preserved for normals (V_r = –95.6 mV), whereas HypoPP fibers may be excitable (V_r = –89 mV) or refractory and inexcitable (V_r = –67.7 mV). Reduction of $[K^+]$ to 3.0 mM (**line a**) results in complete loss of excitability for all HypoPP fibers (–66.3 mV) and retained excitability for normal fibers (V_r = –97.8 mV). (Adapted, with permission, from Cannon 2017.)

expressed in skeletal muscle. The resulting mutant Na^+ channels have inactivation defects. Subtle inactivation defects produce myotonia, whereas more pronounced defects result in chronic depolarization and loss of excitability with paralysis (Figure 57–12A–C). Hypokalemic paralysis is caused by missense mutations in the voltage-sensor domains of either Ca^{2+} channels or Na^+ channels in skeletal muscle. Disruption of the voltage-sensor domain allows an influx of ion current through an anomalous pathway, separate from the channel pore (Figure 57–13). This current "leak" in resting fibers produces a susceptibility to depolarization and loss of excitability in low extracellular K^+. A rare form of periodic paralysis that is characterized by weakness, developmental defects, and cardiac irritability is caused by primary mutations in an inwardly rectifying K^+ channel important for the resting potential (Figure 57–13).

In myotonia congenita, muscle stiffness is present from birth and is nonprogressive. Unlike myotonic dystrophy, there is no muscle wasting, permanent muscle weakness, or other organ involvement. Congenital myotonia is a consequence of mutations in the gene coding for the ClC-1 Cl^- channel in skeletal muscle membrane (Figure 57–14). The resultant decrease

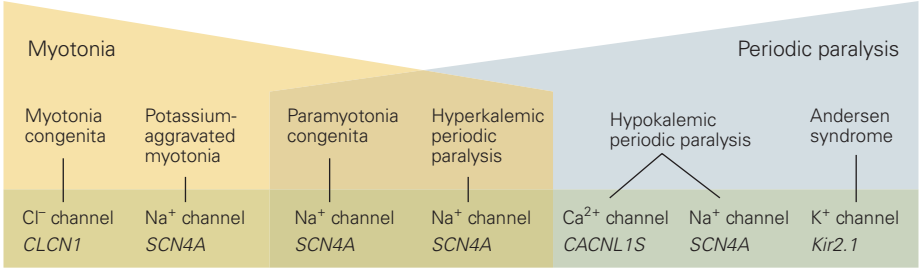


Figure 57–14 The myotonias and periodic paralyses are caused by mutations in genes that code for diverse voltage-gated ion channels in the skeletal muscle membrane. Some of these channel disorders are characterized only by myotonia, some by periodic paralysis without myotonia, and some by both myotonia and paralysis. Some clinical disorders (eg, hypokalemic periodic paralysis) can arise from defects in different channels in different individuals.