cataracts, endocrinopathy, and cardiomyopathy. It affects about 1 in 10,000 individuals. Myotonia, a sustained involuntary contraction of muscles, is a key feature of the disease. Some patients present with "*congenital myotonia,*" marked by severe manifestations in infancy.

Pathogenesis. The disease is caused by expansions of CTG triplet repeats in the 3′-noncoding region of the myotonic dystrophy protein kinase (*DMPK*) gene, but precisely how this genetic aberration produces the disease phenotype is unknown. The correlation between the length of expansion and disease severity is variable compared to some other triplet repeat expansion disorders like Huntington disease (Chapter 28). Experimental studies suggest that the skeletal muscle phenotype stems from a "toxic" gain-of-function caused by the triplet repeat expansion. Specifically, the expanded CUG-repeats in the *DMPK* mRNA transcript appear to bind and sequester a protein called *muscleblind-like-1*, which has an important role in RNA splicing. This inhibits muscleblind-like-1 function, leading to missplicing of other RNA transcripts, including the transcript for a chloride channel called *CLC1*. It is believed that the resulting deficiency of CLC1 is responsible for the characteristic myotonia. In support of this scenario, one rare form of congenital myotonia is caused by germ line loss-of-function mutations in *CLC1,* indicating that CLC1 is required for normal muscle relaxation.

Emery-Dreifuss Muscular Dystrophy

Emery-Dreifuss muscular dystrophy (EMD) is caused by mutations in genes that encode nuclear lamina proteins. Clinically, it is marked by a triad consisting of slowly progressive humeroperoneal weakness, cardiomyopathy associated with conduction defects, and early contractures of the Achilles tendon, spine, and elbows. The X-linked form (EMD1) and the autosomal form (EMD2) are caused by mutations in the genes encoding emerin and lamin A/C, respectively, both of which localize to the inner face of the nuclear membrane. It is hypothesized that these proteins help maintain the shape and mechanical stability of the nucleus during muscle contraction. They may also influence gene expression by affecting chromatin organization in the nucleus. How defects in these proteins produce the observed phenotypes is unknown.

Fascioscapulohumeral Dystrophy

Fascioscapulohumeral dystrophy is associated with a characteristic pattern of muscle involvement that includes prominent weakness of facial muscles and muscles of the shoulder girdle. It is an autosomal dominant disease affecting about 1 in 20,000 individuals.

Pathogenesis. The pathogenesis of fascioscapulohumeral dystrophy is complex and only partly understood. It is established that the disease involves overexpression of a gene called *DUX4* that is located in a region of subtelomeric repeats on the long arm of chromosome 4. What remains unclear is the mechanism and consequences of *DUX4* overexpression. Some individuals with fascioscapulohumeral dystrophy inherit an abnormally small number of subtelomeric repeats. Each repeat carries a copy of the *DUX4* gene, and it appears that deletion of flanking repeats causes changes in chromatin that "derepress" the remaining copies of *DUX4* thus leading to its overexpression. However, the reduction in repeats by itself is not sufficient to produce the disease; instead, the disease is confined to those who also inherit certain single nucleotide polymorphisms (SNPs) at positions immediately 3′ of the *DUX4* coding sequence. Only when the SNPs and the repeat contractions are both present is *DUX4* expressed at high enough levels to be pathogenic. Other individuals have a normal number of repeats and possibly have other mechanisms of *DUX4* overexpression. *DUX4* encodes a transcription factor, suggesting that the disease ultimately results from the overexpression of DUX4 target genes.

Limb-Girdle Muscular Dystrophy

Limb-girdle muscular dystrophies are a heterogeneous group of at least six autosomal dominant and 15 autosomal recessive entities. Their overall incidence is 1 in 25,000 to 50,000 individuals. **As indicated by the name, all forms are characterized by muscle weakness that preferentially involves proximal muscle groups.** Both the age of onset and the disease severity are highly variable. The causative mutations involve genes that participate in diverse cellular functions, making it difficult to discern a unifying mechanism of disease pathogenesis. Based on current knowledge, the implicated genes can be grouped according to function as follows:

- Genes encoding structural components (sarcoglycans) of the dystrophin glycoprotein complex
- Genes encoding enzymes that are responsible for glycosylation of α-dystroglycan, a component of the dystrophin glycoprotein complex
- Genes encoding proteins that associate with the Z-disks of sarcomeres
- Genes encoding proteins involved in vesicle trafficking and cell signaling
- Genes that seemingly stand alone, such as those encoding the protease calpain 3 and lamin A/C (which is also mutated in some patients with Emery-Dreifuss muscular dystrophy)

Diseases of Lipid or Glycogen Metabolism

Many inborn errors of lipid or glycogen metabolism affect skeletal muscle. These disorders tend to produce one of two general patterns of muscle dysfunction. In some, patients become symptomatic only with exercise or fasting, which may produce severe muscle cramping and pain, or even extensive muscle necrosis (*rhabdomyolysis*). Other disorders of this type result in slowly progressive muscle damage, without episodic manifestations. Listed below are some examples in this group of muscle diseases:

- *Carnitine palmitoyltransferase II deficiency* is the most common disorder of lipid metabolism to cause episodic muscle damage with exercise or fasting. The defect in this disorder impairs the transport of free fatty acids into mitochondria.
- *Myophosphorylase deficiency (McArdle disease)* is one of the more common glycogen storage diseases affecting skeletal muscle; it also results in episodic muscle damage with exercise.
- *Acid maltase deficiency* results in impaired lysosomal conversion of glycogen to glucose, causing glycogen to