CHAPTER

43

Limb-Girdle Muscular Dystrophies

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The limb-girdle muscular dystrophies (LGMD) are a heterogeneous group of genetically determined myopathies characterized by progressive weakness and atrophy involving predominantly proximal muscle groups.[1,2] These diseases affect populations worldwide, and have widely variable age of onset, rate of progression, and severity. Both autosomal recessive and dominant forms are recognized. LGMDs were initially identified as a separate group to differentiate them from X-linked or facioscapulohumeral muscular dystrophies. However, genetic studies and other advanced diagnostic tools have documented that LGMD encompasses many distinct myopathies with different inheritance patterns and pathogenetic mechanisms. Therefore, differential diagnosis of the different types of LGMD is not achievable with clinical evaluation alone, and requires the support of DNA and protein analyses. Exclusion diagnostic criteria for LGMD are also useful, such as evidence of abnormal staining or deficiency of dystrophin on muscle biopsies, or evidence of metabolic or neurogenic abnormalities. Furthermore, as many of the proteins involved interact, the primary defect of one of these proteins is often associated with the loss of others, presenting a challenge where the diagnosis is based on immuno and biochemical findings only.

After the discovery that components of the dystrophin-glycoprotein complex (DGC) are implicated in the pathogenesis of LGMD,[3] within a relatively short time a large number of genes have been identified as responsible for different forms of LGMD. Currently, 15 types can be recognized, and the present classification of LGMD is based both on mode of inheritance and gene involved (Table 43–1).

AUTOSOMAL DOMINANT LIMB-GIRDLE MUSCULAR DYSTROPHIES (LGMD1)

Only a relatively small percentage of LGMD (approximately 10%) is transmitted by autosomal dominant inheritance. Common features of this class of disease are late onset, relatively mild phenotype, and slow progression. The serum creatine kinase (CK) levels are also lower than in the recessive forms of LGMD. Five genes have already been mapped, but genetic exclusion studies suggest that others may exist.

LGMD1A

Mutations in the myotilin gene (5q22–q34) have been identified in one North American family of German descent with LGMD1A (Hauser et al, 2000). This late-onset, slowly progressive disease is characterized by weakness of the hip and shoulder girdles and dysarthric speech. CK levels are elevated 1.6- to 9-fold. Affected muscles show a large number of autophagic vesicles with rimmed vacuoles. Z-line streaming similar to that seen in nemaline myopathy is also observed.

Myotilin is a sarcomeric protein that binds to α-actinin and is associated with the Z-line.[4] In muscle biopsies from affected individuals, myotilin appears correctly localized to the Z-line, but it is not clear whether the protein is a product of the normal or the mutated allele. Failure to link to α-actinin is probably not the cause of the muscle pathology, since the mutant myotilin binds α-actinin as well as the wild-type protein. Myotilin may play a role in anchoring the myofibrils to the plasma membrane through its interaction with γ-filamin, which,

TABLE 43–1. Limb-Girdle Muscular Dystrophies: Gene Location and Proteins Involved

Autosomal Dominant Limb-Girdle Muscular Dystrophies

Disease	Gene Location	Gene (protein)	References
LGMD1A	5q22–q34	MYOT (myotilin)	Speer et al. *Am J Hum Genet* 1992;50:1211–1217
			Hauser et al. *Hum Mol Genet* 2000;9:2141–2147
LGMD1B	1q11–q21	LMNA (lamin A/C)	Muchir et al. *Hum Mol Genet* 2000;9:1453–1459
LGMD1C	3p25	CAV3 (caveolin 3)	Minetti et al. *Nat Genet* 1998;18:365–368
			McNally et al. *Hum Mol Genet* 1998;7:871–877
LGMD1D	6q23	?	Messina et al. *Am J Hum Genet* 1997;61:909–917
LGMD1E	7q	?	Speer et al. *Am J Hum Genet* 1999;64:556–562

Autosomal Recessive Limb-Girdle Muscular Dystrophies

Disease	Gene Location	Gene (protein)	References
LGMD2A	15q15.1–q21.1	CAPN3 (calpain 3)	Beckmann et al. *CR Acad Sci III* 1991;312:141–148
			Young et al. *Genomics* 1992;13:1370–1371
			Richard et al. *Cell* 1995;81:27–40
			Richard et al. *Am J Hum Genet* 1997;60:1128–1138.
LGMD2B	2p13	DYSF (dysferlin)	Bashir et al. *Hum Mol Genet* 1994;3:455–457
			Bashir et al. *Nat Genet* 1998;20:37–42
			Liu et al. *Nat Genet* 1998;20:31–36
LGMD2C	13q12	SGCG (γ-sarcoglycan)	Ben Othmane et al. *Nat Genet* 1992;2:315–317
			Azibi et al. *Hum Mol Genet* 1993;2:1423–1428
			Noguchi et al. *Science* 1995;270:819–822
			McNally et al. *Am J Hum Genet* 1996;59:1040–1047
			Piccolo et al. *Hum Mol Genet* 1996;5:2019–2022
LGMD2D	17q12–q21.33	SGCA (α-sarcoglycan)	Roberds et al. *Cell* 1994;78:625–633
			Piccolo et al. *Nat Genet* 1995;10:243–245
			Passos-Bueno et al. *Hum Mol Genet* 1995;4:1163–1167
			Ljunggren et al. *Ann Neurol* 1995;38:367–372
			Carrié et al. *J Med Genet* 1997;34:470–475
LGMD2E	4q12	SGCB (β-sarcoglycan)	Lim et al. *Nat Genet* 1995;11:257–265
			Bonnemann et al. *Nat Genet* 1995;11:266–273
LGMD2F	5q33–q34	SGCD (δ-sarcoglycan)	Passos-Bueno et al. *Hum Mol Genet* 1996;5:815–820
			Nigro et al. *Nat Genet* 1996;14:195–198
LGMD2G	17q11–q12	TCAP (telethonin)	Moreira et al. *Am J Hum Genet* 1997;61:151–159
			Moreira et al. *Nat Genet* 2000;24:163–166
LGMD2H	9q31–q34.1	TRIM32 (TRIM32)	Weiler et al. *Am J Hum Genet* 1998;63:140–147
			Frosk et al. *Am J Hum Genet* 2002;70:663–672
LGMD21	19q13.3	FKRP (fukutin-related protein)	Driss et al. *Neuromuscul Disord* 2000;10:240–246
			Brockington et al. *Hum Mol Genet* 2001;10:2851–2859
LGMD2J	2q	TTN (titin)	Haravuori et al. *Neurology* 2001;56:869–877

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in turn, may bind to γ- and δ-sarcoglycans. Mutations in α-tropomyosin, another protein that localizes to the Z-line, have been shown to cause nemaline myopathy (NEM2). Interestingly, α-tropomyosin also binds α-actinin, and missense mutations in the gene result in autosomal dominant nemaline myopathy with disruption of the Z-line.[5] The similarity between these two disorders raises the possibility that LGMD1A might have

been misdiagnosed as late-onset nemaline myopathy. Although the locus for LGMD1A overlaps with a distinct clinical disorder characterized by velopharyngeal weakness and involvement of the distal musculature (VCPDM), genetic analysis of VCPDM patients did not reveal mutations in the myotilin gene (Hauser et al, 2000).

LGMD1B

LGMD1B is a slowly progressive disorder characterized by weakness of proximal leg muscles, mild or late contractures, and atrioventricular cardiac conduction disturbances that worsen with time. CK levels are normal or slightly elevated. The disease is caused by mutations in the *LMNA* gene on chromosome 1q11–1q21. The gene encodes two proteins of the nuclear envelope, lamins A and C (lamin A/C), which are organized in dimers and interact with chromatin and integral proteins of the inner nuclear membrane.[6] Thus, perturbation of the nuclear architecture may be what triggers muscle pathology. Mutations in the *LMNA* gene are also associated with autosomal dominant Emery-Dreifuss muscular dystrophy (AD-EDMD). This disorder differs from LGMD1B because of the presence of early elbow and ankle contractures, predominant humeroperoneal muscle wasting, and severe cardiomyopathy with conduction defects that may be present at the onset or occur at any age. Furthermore, the *LMNA* gene is implicated in cardiomyopathies with conduction defect (DCM-CD), Dunningan-type familial partial lipodystrophy (FPLD), axonal Charcot-Marie-Tooth type 2 (AR-CMT2A),[7] and mandibuloacral dysplasia (MAD).[8] Further analysis of the phenotype-genotype correlation will be necessary to clarify the varying phenotypes observed in these allelic diseases.

LGMD1C

Mutations in the caveolin-3 gene associated with significant reduction of protein expression cause LGMD1C (McNally et al, 1998; Minetti et al, 1998). A number of missense mutations have also been reported in patients with LGMD, where neither the expression nor the localization of caveolin-3 were altered. As the same sequence variations were found in normal controls, these amino acid substitutions represent polymorphisms and are not likely to cause autosomal dominant muscular dystrophy.[9] Patients with mutations in the *CAV3* gene have normal motor milestones, but develop myopathy during childhood, with calf hypertrophy and mild to moderate proximal muscle weakness. A characteristic feature of LGMD1C is the occurrence of muscle cramps after exercise. CK levels are elevated 4- to 25-fold. The progression of the disease is variable.

Caveolin-3 is the muscle-specific member of a family of proteins localized at small invaginations of the plasma membrane (caveolae) that are believed to be involved in signal transduction.[9] Mutations in caveolin-3 give rise to unstable high molecular mass aggregates composed of normal and mutated protein that are retained in the Golgi complex. Although caveolin-3, like dystrophin, localizes at the sarcolemma, it is not an integral part of the DGC. However, caveolin-3 has been shown to interact with the dystrophin-binding site of β-dystroglycan, suggesting that it may regulate the interaction of β-dystroglycan with dystrophin.[10] Caveolin-3 also interacts with neuronal nitric oxide synthase (nNOS), and binding results in loss of nNOS activity. Severe reduction in the number of caveolae has been described at the sarcolemma of LGMD1C patients. This demonstrates that caveolin-3 plays an important role in the formation of these structures in skeletal muscle. Furthermore, the T-tubule system is profoundly altered in LGMD1C muscle fibers.[11]

Mutations in *CAV3* have been demonstrated in LGMD1C, but also in hyperCKemia, distal myopathy, and rippling muscle disease. The same mutations are associated with different phenotypes in the same families, but there are few large families with caveolin-3 mutations. Caveolin-3 may also have a role in the pathogenesis of other muscular dystrophies, as muscle from patients with Duchenne muscular dystrophy (DMD) shows overexpression of caveolin-3 along with increased number of caveolae.[9] In addition, abnormal localization of dysferlin has been reported in muscle from patients with LGMD1C, suggesting a structural or functional interaction between these proteins.[12]

LGMD1D (FDC-CDM)

LGMD1D is an autosomal dominant adult-onset disorder linked to chromosome 6q23 (Messina et al, 1997). Features include proximal weakness and dystrophic changes in the muscle biopsy, such as variable fiber size and increased connective tissue. CK levels are elevated twofold to fourfold, and the clinical progression is slow. Cardiac involvement is significant, with a high frequency of arrhythmia and congestive heart failure. Sudden death without prior cardiac symptoms has also been reported. In the single French-Canadian family described, males were more severely affected with both skeletal and cardiac disease. A candidate gene is currently being investigated.

LGMD1E

A new locus for LGMD has been identified on chromosome 7q in two families with autosomal dominant inheritance (Speer et al, 1999). Affected individuals present in early adulthood with proximal weakness involving primarily the lower limbs. Serum CK levels are normal to elevated threefold. Linkage analysis to candidate genes is currently ongoing.

AUTOSOMAL RECESSIVE LIMB-GIRDLE MUSCULAR DYSTROPHIES (LGMD2)

Ten different loci have been linked to autosomal recessive LGMD (LGMD2), and the genes have been identified. However, linkage analysis in a number of families still excludes all known loci, indicating that other genes must be responsible for the disease. The recessive LGMDs are more frequent than the dominant forms and usually have earlier onset. LGMD2A is probably the most common, accounting for about 30% of cases, whereas LGMD2G, 2H, and 2J have been described in only a few families. Genes responsible for LGMD2C–F encode components of the sarcoglycan complex, and the recently identified gene for LGMD2I encodes a putative glycosyltransferase involved in posttranslational processing of α-dystroglycan. Thus, many of the LGMD2 types involve members of the DGC.

LGMD2A

LGMD2A is caused by mutations in the gene coding for the muscle-specific calcium-dependent protease calpain 3 located on chromosome 15 (Richard et al, 1995). Mutations in the gene were originally identified in families of French descent on La Réunion Island and subsequently found in numerous individuals worldwide. Calpainopathy is characterized by variable onset that ranges from 2 to 40 years, but is most common in the early teens. The progression of the disease is slow, and muscle impairment is highly selective, affecting more severely the lower extremities and sparing the hip abductors. CK levels are elevated 7- to 80-fold.

Calpain 3 has three unique regions (NS, IS1, and IS2) that confer its muscle specificity. The protein interacts with titin via one of these muscle-specific sequences, IS2, which also contains a nucleus translocation signal-like sequence. A study of muscle biopsies from calpainopathy patients showed more apoptotic nuclei than in biopsies from patients with other muscular dystrophies. This was associated with a perturbation of the IκBα/NF-κB pathway.[13] At present, several hypotheses have been formulated for the function of calpain 3 in skeletal muscle, and the mechanism that generates muscular dystrophy in the absence of this protein could be a combination of a number of factors. As calpain 3 is found in both nucleus and cytoplasm, it may play a role in the control of the expression of muscle-specific transcription factors, thereby regulating muscle differentiation. Furthermore, the secondary reduction of calpain 3 in muscle biopsies from LGMD2B patients[14] suggests that this protein may be involved in the process of membrane resealing and repair.

LGMD2B

Dysferlin, the gene mutated in LGMD2B, is located at chromosome 2p13 (Bashir et al, 1998; Liu et al, 1998). Mutations in the dysferlin gene are also responsible for Miyoshi myopathy, a distal muscular dystrophy.[15] As the same mutations have been associated with proximal and distal phenotypes, modifier genes may produce the observed clinical heterogeneity. Patients have normal motor development and function early in life. Onset of LGMD2B is in the late childhood to early adult age. Serum CK can be very high (elevated 10- to 72-fold), but the rate of progression is slow. After most of the lower-limb muscles become involved, the upper extremities also exhibit weakness. Dystrophic signs and inflammatory infiltrates are observed both in muscle from LGMD2B patients and from the SJL mouse, a naturally occurring model of dysferlinopathy. It is not clear whether the inflammation contributes to the pathology or is merely a secondary phenomenon.[16]

Dysferlin is a member of the FER-1-like protein family. It is characterized by a C-terminus transmembrane domain and multiple C2 domains, which are predicted to play a role in transduction pathways and membrane trafficking. The homologous FER-1 has been identified in *Caenorhabditis elegans,* where it is involved in spermatogenesis. In humans, dysferlin is more widely distributed, although it predominates in skeletal muscle, where it localizes at the sarcolemma and in intracellular vesicles. A dysferlin point mutation responsible for muscular dystrophy was expressed in cultured cells where it reduced the calcium-sensitive phospholipid-binding ability of dysferlin.[17] These data indicate that dysferlin may play a role in regeneration and repair. Caveolin-3 potentially interacts with dysferlin, suggesting that one function of dysferlin may be to maintain the signaling functions of caveolae.

SARCOGLYCANOPATHIES

Involvement of the α, β, γ, and δ components of the sarcoglycan complex is responsible for LGMD2C–F.[3] The sarcoglycans (SGs) are members of a group of proteins associated with dystrophin, the protein affected in Duchenne and Becker muscular dystrophies. The DGC is organized in three subcomplexes: the cytoskeletal proteins, dystrophin, and syntrophins; the dystroglycans (α and β); and the sarcoglycan-sarcospan subcomplex.[18] Many other proteins have recently been shown to associate with the DGC, including dystrobrevin and neuronal nitric oxide synthase. The interaction of the DGC with the extracellular matrix provides a structural scaffold that may protect the muscle fibers from damage caused by contraction. Transmembrane glycoproteins α-, β-, γ- and δ-SG share a number of features: They all contain a small intracellular domain, a single transmembrane domain, and a large extracellular domain that contains potential N-glycosylation sites. Expression of α-SG is limited to striated muscle, while β-, γ-, and δ-SG are also expressed in smooth muscle in association with ε-SG, a glycoprotein homologous to α-SG.[19] Recent evidence suggests that the vascular smooth muscle SG complex is involved in

the cardiac muscle pathology observed in δ-, β-, and γ-, but not α-sarcoglycanopathies.[20] Mutations in α-sarcoglycan (2D) are the most common, whereas mutations in δ-sarcoglycan (2F) are rare. LGMD2C–F present a number of common characteristics: The clinical phenotype is characterized by progressive skeletal muscle weakness, with intra- and interfamilial variability in age of onset, rate of progression, and severity. Symptoms at onset include weakness, toe walking, and muscle pain, with severe involvement of shoulder girdle and hamstrings. CK levels are very high. When there is a mutation in one of the SG genes, there is also a secondary reduction of the other SGs, accompanied in some cases by less severe reduction of dystrophin. Immunostaining of muscle biopsies with specific antibodies may be suggestive of the gene primarily involved, but correct diagnosis requires genetic analysis.

LGMD2C (γ-Sarcoglycan)

Previously labeled "Duchenne-like muscular dystrophy" or "severe childhood autosomal recessive muscular dystrophy," LGMD2C was first described in North Africa, and in the European gypsy population (Azibi et al, 1993; Ben Othmane et al, 1992; Piccolo et al, 1996). The gene responsible for this disorder was localized to chromosome 13, and the defective protein recognized as γ-SG (Noguchi et al, 1995). Patients exhibit predominantly early onset with proximal lower-limb weakness (often sparing the quadriceps muscles) and normal intelligence. Loss of ambulation develops in the early teens, and respiratory failure occurs in the third decade. Cardiac involvement may be present in the later stages of the disease.

LGMD2D (α-Sarcoglycan)

The most common form of sarcoglycanopathy has been mapped on chromosome 17q21, and the protein involved is α-SG (Roberds et al, 1994). The original description of this disorder was in Algerian families, with subsequent identification in Brazilian families; however, α-sarcoglycanopathy occurs worldwide (Passos-Bueno et al, 1993; Piccolo et al, 1995). The most commonly reported mutation, independent of ethnicity, is Arg77Cys (Carrié et al, 1997). This form of muscular dystrophy has variable severity, ranging from early onset with rapidly progressive weakness to late onset with ambulation preserved throughout life. A correlation exists between type of mutation, levels of α-SG expression, and disease severity. Null mutations result in complete loss of the protein and a Duchenne muscular dystrophy–like phenotype. Progression of the disease is usually faster in patients with early onset, and they are usually confined to a wheelchair by age 15 years.

LGMD2E (β-Sarcoglycan)

Defects in the β-SG gene are responsible for LGMD2E (Bonnemann et al, 1995; Lim et al, 1995). A missense mutation in this gene was originally described in northern and southern Indiana Amish families. Mutations in the β-SG gene are now reported in other populations worldwide. A wide range of clinical severity has been observed in LGMD2E patients. The age of onset varies from early childhood to adult life with proximal weakness and enlarged calves. Wheelchair dependence may occur in the early teens, but some patients maintain independent ambulation into their sixth decade. Intrafamilial variability for age of onset and progression has been reported as a common feature of LGMD2E.

LGMD2F (δ-Sarcoglycan)

The gene coding for δ-SG is located on chromosome 5q33–34 (Nigro et al, 1996). Mutations in this gene were first identified in families of African-Brazilian descent. Patients with LGMD2F show a severe clinical course with onset within the first decade, loss of independent ambulation in the early teens, and death between 9 and 19 years. Cardiac abnormalities are frequent. Patients carrying dominant mutations in the δ-SG gene may show dilated cardiomyopathy without skeletal muscle involvement. The same gene is spontaneously mutated in the BIO14.6 Syrian hamster, an animal model of cardiomyopathy that displays only minor involvement of skeletal muscle, suggesting the δ-SG gene is a candidate for familial and idiopathic dilated cardiomyopathies as well as LGMD.[21]

LGMD2G

Mutations of the human telethonin gene have recently been shown to cause LGMD2G in three Brazilian families (Moreira et al, 1997, 2000). Besides severe involvement of the proximal muscles in the upper and lower limbs, these patients have early involvement of distal muscles, foot drop, mildly elevated serum CK levels (3- to 30-fold), and rimmed vacuoles in muscle biopsies. Age of onset ranges from 9 to 15 years, and 40% of patients become nonambulatory in the third or fourth decade of life. Cardiac involvement may be present.

Telethonin is a sarcomeric protein expressed at the Z-line in skeletal and cardiac muscle.[4] Telethonin is a substrate of the serine kinase domain of titin, which phosphorylates the carboxy-terminal domain of telethonin in early differentiating myocytes. The transcript in mouse is developmentally regulated in both cardiac and skeletal muscle and is downregulated after denervation. Telethonin may be involved in myofibril assembly and turnover; however, further studies are required to clarify the pathogenetic mechanisms of LGMD2G.

LGMD2H

Originally described in the Hutterite population of Manitoba (Weiler et al, 1998), LGMD2H has late onset and a mild, slowly progressive course. In addition to

weakness of proximal limb muscles, patients may present weakness of facial muscles as the disease progresses. The gene has been mapped on chromosome 9q31–q34.1 and encodes TRIM32, a putative E3 ubiquitin ligase highly expressed in heart and skeletal muscle (Frosk et al, 2002). The role of E3 ligases involves the labeling of target proteins with ubiquitin, so that the proteins may be tagged for degradation by the proteasome pathway. Mutations in this gene may cause failure to recognize the target proteins, and their accumulation can lead to muscle disease. At present, there is no evidence for protein accumulation in muscle; however, further studies may clarify this issue.

LGMD2I

The gene for fukutin-related protein (FKRP), responsible for LGMD2I, maps on chromosome 19q13.3 (Brockington et al, 2001; Driss et al, 2000). FKRP was identified through homology to fukutin, the putative glycosyltransferase involved in the pathogenesis of Fukuyama congenital muscular dystrophy. Mutations in the *FKRP* gene were first found in a form of congenital muscular dystrophy (MDC1C) with secondary reduction in laminin α2 and abnormal glycosylation of α-dystroglycan (α-DG).[22] The features of MDC1C are severe weakness, wasting of the shoulder girdle musculature, and hypertrophy and weakness of other muscles such as calf and thigh. Macroglossia has also been reported. Several patients show progressive respiratory failure and cardiomyopathy. Individuals with LGMD2I present a similar, though milder, phenotype. The age of onset varies between 0.5 to 27 years, and progression is slow with a large range of phenotypic severity. A significant number of families have mutations in the *FKRP* gene, and many other patients unlinked to the known LGMD loci may carry mutations in this gene.

FKRP is a ubiquitous protein expressed at highest levels in skeletal muscle, heart, and placenta. The amino-terminus sequence targets FKRP to the Golgi complex, where it colocalizes with α-mannosidase II. The homology to fukutin strongly suggests an enzymatic role for FKRP in the glycosylation pathway. Analysis of muscle from patients affected with mild LGMD2I has revealed a selective deficit of higher molecular weight α-DG, and loss of its laminin-binding properties. The dystroglycan complex in muscle forms an axis that connects the intracellular cytoskeleton to the extracellular matrix through direct binding of α-DG to laminin and β-DG to dystrophin.[23] Dystroglycan is the product of the *Dag1* gene, which, through posttranslational processing generates two noncovalently linked proteins: the extracellular heavily glycosylated α-DG, and the transmembrane β-DG. The nature of the carbohydrate moiety of α-DG has not been clarified, but it is clear that altered glycosylation results in loss of laminin binding. A selective reduction in α-DG staining was also observed in patients with MDC1C and LGMD2I, indicating that mutations in the FKRP gene may affect glycosylation of α-DG. These findings underscore the existence of a common pathogenetic mechanism in MDC1C/LGMD2I, Fukuyama congenital muscular dystrophy, and MEB, in which the affected genes are putative glycosyltransferases. Mutations in different genes coding for enzymes involved in the glycosylation pathway of α-DG may render the protein unable to interact with its ligands, thereby perturbing the central link between extracellular matrix and cytoskeleton and leading to sarcolemmal instability and muscular dystrophy.[24]

LGMD2J

Tibial muscular dystrophy is a mild autosomal dominant disease involving mostly distal muscles and caused by mutations in the titin gene.[25] However, homozygous patients have also been described, presenting proximal early-onset limb-girdle muscular dystrophy with high serum CK levels and secondary deficiency of calpain 3 (Haravuori et al, 2001).

Titin is a large sarcomeric protein that may play a role in the sarcomere assembly and in keeping the myosin filaments in place during contraction cycles.[4] Several ligand-binding sites are present along the protein. Two of the ligands are calpain 3 and telethonin, which are responsible for two other types of LGMD2. The observation that calpain 3 is reduced in heterozygous patients and absent in homozygous LGMD2J suggests that in heterozygotes the binding activity of titin is partially preserved. The loss of activity in homozygous patients results in a phenotype similar to a primary calpainopathy. In support to this hypothesis, apoptotic myonuclei with altered distribution of NF-κB and IκBα are often observed in muscle samples of LGMD2J patients. It is possible that the disease in other LGMD patients with a secondary deficiency of calpain 3 may be due to mutations in titin, and the disease is unnoticed in heterozygous parents due to the mild phenotype.

CONCLUSION

Mutations in the genes involved in LGMD produce allelic heterogeneity and a broad array of phenotypes. The different characteristics of the proteins involved in LGMD (Fig. 43–1) are suggestive of diverse pathogenetic mechanisms. Perturbations of the components of the DGC affect the link between the cytoskeleton and the extracellular matrix, leading to loss of sarcolemmal integrity, and muscular dystrophy. Impaired membrane repair and resealing of damaged muscle fibers may be related to the pathogenesis of LGMD due to dysferlin and calpain 3 mutations. The identification of a group of sarcomeric proteins involved in dystrophic changes indicates that disturbance of the myofibril assembly may be responsible for LGMD. Finally, the linkage of the putative ubiquitin ligase TRIM32 to an LGMD locus may suggest that protein degradation abnormalities

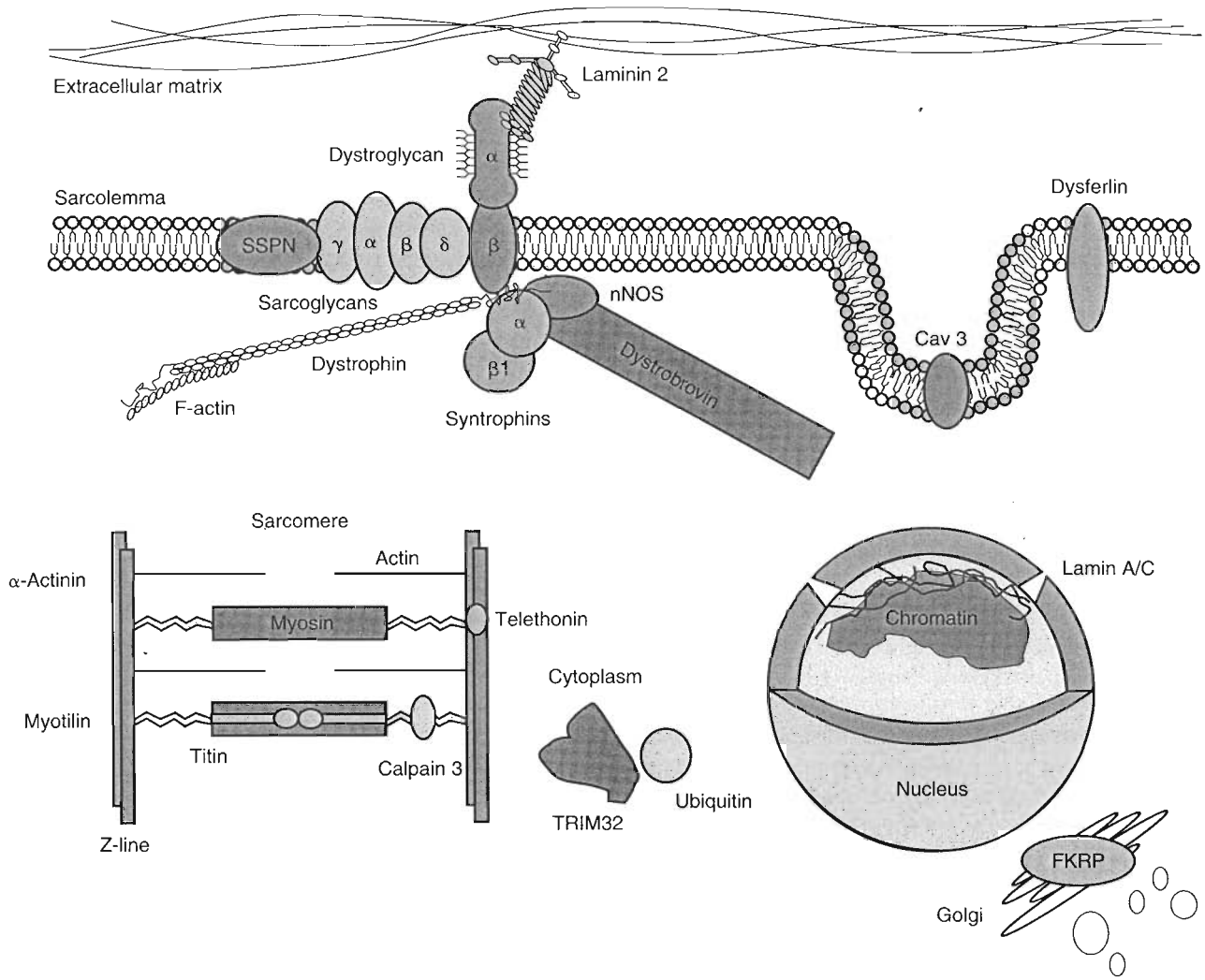

FIGURE 43–1. Schematic representation of the proteins involved in the pathogenesis of LGMD. Sarcolemmal proteins comprise sarcoglycans, caveolin 3, and dysferlin. Titin, telethonin, and myotilin are sarcomeric proteins. Lamin A/C is found at the nuclear envelope. FKRP localizes in the Golgi complex. TRIM32 may be involved in the ubiquitination pathway.

may also lead to muscular dystrophy. Although advances have been significant, much remains to be learned about the functions of these proteins and the pathologic consequences of their deficiency. The analysis of spontaneous mutants and the generation of animal models lacking proteins affected in the various LGMD pathologies are shedding light on the pathogenetic mechanisms involved and providing insight on future therapies for the treatment of these diseases.

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*Parenthetical reference citations may be found in Table 43–1.

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