The sarcoglycan complex in limb-girdle muscular dystrophy
Leland E. Lim and Kevin P. Campbell

The involvement of the sarcoglycan complex in the pathogenesis of muscular dystrophy is becoming increasingly clear. Sarcoglycan gene mutations lead to four forms of autosomal recessive limb–girdle muscular dystrophy. Recent progress has been made with the identification of novel mutations and their correlations with disease. Through this research, a better understanding of the molecular pathogenesis of limb–girdle muscular dystrophy has been gained. Finally, animal models are now being used to study viral-mediated gene transfer for the future treatment of this disease. Curr Opin Neurol 11:443–452. © 1998 Lippincott Williams & Wilkins

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Abbreviations
CFTDR cystic fibrosis transmembrane conductance regulator
DGC dystrophin-glycoprotein complex
LGMD limb–girdle muscular dystrophy
SCARMD severe childhood autosomal recessive muscular dystrophy

Introduction
The term 'muscular dystrophy' describes a group of diseases characterized by hereditary progressive muscle weakness and degeneration. Several muscular dystrophies, including certain types of limb–girdle muscular dystrophy (LGMD), are caused by mutations in genes that encode sarcolemmal proteins. LGMD is genetically and clinically heterogeneous; it may be inherited in an autosomal dominant or recessive manner, and may have different rates of progression and severity. The unifying theme among the LGMDs is the initial involvement of the shoulder and pelvic girdle muscles, with relative sparing of most other muscle groups [1,2].

The nomenclature for LGMD has changed over the years; other terms for this condition have included Duchenne-like muscular dystrophy and severe childhood autosomal recessive muscular dystrophy (SCARMD). However, as understanding of the genetic basis of this varied entity progressed, an agreement in nomenclature was achieved [3]; LGMD1 refers to autosomal dominant forms [4–8] and LGMD2 refers to the recessive forms [9–28] (Table 1).

Among LGMD2 are four distinct subtypes caused by mutations in sarcoglycan glycoproteins: LGMD2D (α-sarcoglycan) [15–17], LGMD2E (β-sarcoglycan) [18,19], LGMD2C (γ-sarcoglycan) [20–24], and LGMD2F (δ-sarcoglycan) [25,26]. Together, these glycoproteins form a subcomplex within the larger dystrophin–glycoprotein complex.

Dystrophin–glycoprotein complex
The dystrophin-glycoprotein complex (DGC) is a sarcolemmal protein complex that is expressed at high levels in striated muscle [29–32]. The integral components of the DGC include dystrophin, a large, rod-shaped cytoskeletal protein that binds F-actin [33–35,36*]; α-dystroglycan and β-dystroglycan, which bind the G domain of laminin-2 and the cysteine-rich region of dystrophin [37–39], respectively; the syntrophins, intracellular proteins that bind the C-terminus of dystrophin [40,41]; sarcospan, a four-transmembrane domain protein [42*]; and the sarcoglycans, as described below [15,18,19,22,43–46] (Fig. 1). These proteins represent the ‘core’ DGC; however, there are other proteins that are known to be associated with this complex, but are not found in pure DGC preparations. In addition to
Table 1. Chromosomal locations and disease genes of the limb–girdle muscular dystrophies (LGMDs)

<table>
<thead>
<tr>
<th>Disease</th>
<th>Chromosomal location</th>
<th>Gene</th>
<th>Gene product</th>
<th>References</th>
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<tr>
<td>Autosomal</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
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<td>SGCA</td>
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<td>Unknown</td>
<td>Unknown</td>
<td>[28]</td>
</tr>
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</table>

Figure 1. The dystrophin–glycoprotein complex

Figure 2. The sarcoglycans

As a group, the sarcoglycans have no homology to any other known proteins. However, among themselves they bear certain striking similarities (Fig. 2). All four skeletal muscle sarcoglycans have single transmembrane domains, relatively small intracellular domains, and large extracellular domains. Their molecular weights fall within a narrow range of 35–50 kDa, and are all glycosylated on at least one residue. All sarcoglycans contain exactly five cysteine residues in the extracellular domain, with β-sarcoglycan, γ-sarcoglycan, and δ-sarcoglycan having these residues clustered towards the end of the extracellular domain. One difference among the sarcoglycans is that α-sarcoglycan contains a 23-amino-acid signal sequence, which results in an extracellular N-terminus, unlike β-sarcoglycan, γ-sarcoglycan, and δ-sarcoglycan, which all have extracellular C-termini. Secondary structure analysis of each sarcoglycan protein [64] revealed the presence of several β-pleated sheets and α-helices. The primary structures of the sarcoglycans are highly conserved across laminin-2 and F-actin, there is evidence that neuronal nitric oxide synthase [47] and an alternatively spliced protein called dystrobrevin [48–50] interact with components of the DGC. Although caveolin-3 was hypothesized to be associated with the DGC [51,52], recent evidence indicates that it is not an integral component of the DGC [53]. Through its interactions with the extracellular matrix and the cytoskeleton, it has been imputed that at least one function of the DGC is to confer stability to the muscle cell membrane, and to protect muscle fibers from contraction-induced damage [54–56]. Indeed, mutations in several DGC components and laminin-2 have been implicated in various forms of human muscular dystrophy [15–19,22,24,26,57–60,61*,62,63].
different mammalian species, suggesting an important role throughout evolution.

Recently, Ettinger et al. [65*] cloned and characterized the complementary DNA for a fifth sarcoglycan, ε-sarcoglycan. ε-Sarcoglycan shares 44% amino acid identity with α-sarcoglycan, and also has a signal sequence and an extracellular N-terminus. McNally et al. [66*] reported that the genomic organization of ε-sarcoglycan is identical to that of α-sarcoglycan, and localized the gene to human chromosome 7q21. As yet, no known muscular dystrophy has been mapped to this region, in contrast to the other sarcoglycans. Although it has considerable homology with the other sarcoglycans, ε-sarcoglycan is distinguished from the other sarcoglycans by its expression pattern. Whereas α-sarcoglycan, β-sarcoglycan, γ-sarcoglycan, and δ-sarcoglycan are expressed either exclusively or predominantly in striated muscle, ε-sarcoglycan is broadly expressed, and appears to be expressed at high levels in lung. This suggests that ε-sarcoglycan may be part of a nonmuscle sarcoglycan complex, possibly with functions similar to those of the DGC.

Sarcoglycan-deficient limb–girdle muscular dystrophy

Subsequent to the initial discovery of the DGC, the hypothesis arose that muscular dystrophy may be caused by mutations in the different DGC components. Several populations with autosomal inheritance of muscular dystrophy had been identified, which excluded diagnoses of X-linked Duchenne and Becker muscular dystrophies. The first evidence for a sarcoglycan complex-specific muscular dystrophy arose in the early 1990s, when a SCARMD (now LGMD2C) population in North Africa was shown to have a deficiency of the 50-kDa component of the DGC [67]. Based on this association, this 50-kDa component was dubbed ‘adhalin’, from the Arabic word for muscle [43].

Linkage analysis of these families localized the SCARMD locus to chromosome 13q12, and this was initially considered to be the location of the adhalin (now α-sarcoglycan) gene as well [20,21]. However, SCARMD was shown to be genetically heterogeneous, as families of Brazilian and European descent did not demonstrate linkage to 13q12 [68–70]. This was the first indication that LGMD would turn out to be a complex disorder, and also highlighted the range of clinical presentations of the disease, as is discussed below. In 1994, Roberds et al. [15] reported the primary structure of human α-sarcoglycan and localized the gene to chromosome 17, thus excluding it as the disease gene of the North African SCARMD population. In the same paper, the authors identified missense mutations in α-sarcoglycan in a European family, which represented the first report of muscular dystrophy caused by mutations in a sarcoglycan gene. Since that initial discovery, mutations in other sarcoglycan genes followed in short order. A homozygous missense mutation in β-sarcoglycan was identified in a large Amish pedigree with LGMD2E [18]; in the same journal, a sporadic case of severe muscular dystrophy with β-sarcoglycan mutations was reported [19]. Simultaneously, the disease gene of the North African LGMD2C population was identified as γ-sarcoglycan [22]. Within a year, δ-sarcoglycan was both characterized and implicated in LGMD2F [26,45,46].

The sarcoglycan proteins have been shown to form a distinct subcomplex within the larger DGC. These glycoproteins are known to be tightly associated with each other, giving the inability to disrupt the complex using detergents such as octyl glucoside [71] and sodium dodecyl sulfate [23], and the ability of certain subunits to be crosslinked with various agents [71]. In addition, a common immunohistochemical finding in sarcoglycan-deficient LGMD is a loss or significant reduction of sarcoglycan components at the sarcolemma [18,19,22,23,26,72], demonstrating that membrane stability or targeting of each sarcoglycan protein is dependent on the integrity of the sarcoglycan complex as a whole. An example of this phenomenon in a LGMD2E patient [18] is illustrated in Fig. 3. There is also evidence that α-dystroglycan is destabilized at the extracellular surface of muscle fibers, suggesting that the sarcoglycan complex may also be closely associated with dystroglycan [73]. This result has been confirmed in the study of the cardiomyopathic hamster, an animal model of LGMD (see Animal models) [74–76]. In addition, subtle abnormalities in dystrophin expression in both LGMD and the cardiomyopathic hamster have been noted [74,77].

Little is known about the functional role of the sarcoglycan complex, other than that its integrity is critical for normal muscle physiology. Extensive analysis of LGMD families has resulted in the identification of several mutations, which cause disease ranging in phenotype from mild impairment with slow progression to severe disability and rapid deterioration. The diversity of mutations in sarcoglycan-deficient LGMD has been best studied in α-sarcoglycan. In two recent studies, 25 different mutations in 31 unrelated families were reported; together with other reports of sporadic mutations, a total of 39 distinct α-sarcoglycan mutations have been identified [16,78**]. The vast majority of mutations are located in the large extracellular domain, and in particular in exon 3, in which 12 different mutations have been found. Exon 3 also is the location of the most prevalent sarcoglycan mutation, Arg77Cys [78**]. In the studies mentioned above, this mutation represented nearly a third of all reported chromosomes. In β-sarcoglycan, most of the identified mutations also occur extracellularly, in exons 3 and 4. Fewer γ-sarcoglycan mutations have been identified, and only
Figure 3. Immunohistochemical analysis of a limb-girdle muscular dystrophy type 2E patient

<table>
<thead>
<tr>
<th>Control</th>
<th>LGMD2E</th>
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<tbody>
<tr>
<td>Dys</td>
<td></td>
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<tr>
<td>α-SG</td>
<td></td>
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<td>β-SG</td>
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<td>γ-SG</td>
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<tr>
<td>δ-SG</td>
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In the control individual, staining for dystrophin and the four sarcoglycan proteins is present at the sarcolemma. In the limb-girdle muscular dystrophy type 2E patient, who has mutations in the β-sarcoglycan gene, all four components are reduced at the sarcolemma. Similar immunohistochemical patterns are found in patients with mutations in α-sarcoglycan, γ-sarcoglycan, or δ-sarcoglycan.

Previously, it was believed that missense mutations would result in mild disease, whereas null mutations or deletions would cause severe phenotypes. However, the growing body of knowledge suggests that this association is not always true. Bönne mann and coworkers described a Brazilian LGMD2E family with a homozygous Arg91Pro mutation and severe muscular dystrophy [84] and a Tunisian family with an Arg91Leu mutation and mild disease [85]. Similarly, Duclos et al. reported an Arg91Cys mutation in an Amish population with relatively mild muscular dystrophy [73]. In addition, there is ample evidence to indicate that a single mutation or combination of mutations may cause LGMD of varying severity. LGMD2D patients homozygous for the highly prevalent Arg77Cys mutation have been identified with both mild and severe muscular dystrophy [77, 86]. In a series of LGMD2D patients, Carrière et al. [78**] identified two compound heterozygotes for Arg34His/Arg77Cys mutations, of which one had severe muscular dystrophy, whereas the other had an intermediate phenotype. Similar results were found with other compound heterozygotes with null/Arg77Cys and Arg77Cys/Arg284Cys mutations. McNally et al. [87] described four patients from a North African population homozygous for a Δ521-T deletion in γ-sarcoglycan. Three patients presented with severe muscular dystrophy, whereas one had a much milder clinical course. Recently, Angelini et al. [88**] reported two siblings with a homozygous α-sarcoglycan Arg284Cys mutation; one presented with mild disease, the other was asymptomatic with only increased serum creatine kinase levels. Interestingly, the affected sibling was treated with deflazacort,
with apparent functional benefit. This suggests that LGMD may be treated symptomatically with steroids to improve muscle function, at least in the less severe cases. Further study of this possibility will be of immense interest to clinicians.

The reasons for this variability are not understood. One emerging hypothesis is the idea that the amount of residual expression of the sarcoglycan complex may affect severity [78**,89**]. That is, if a patient has at least low levels of sarcoglycan complex expression, the rate of progression may be somewhat attenuated compared with that in a person with complete deficiency. Thus, in the patients with residual expression, some degree of normal muscle function may be retained, despite the presence of an improperly functioning sarcoglycan complex. One study of LGMD patients [77] demonstrated a possible correlation; however, exceptions were noted within this study. In another study of LGMD2D patients, Eymard et al. [89**] demonstrated a relationship between residual α-sarcoglycan expression and disease severity. However, at least one case of early-onset severe LGMD2D with only partial α-sarcoglycan deficiency has been reported, which also argues against this correlation [90]. These recent reports of partial sarcoglycan complex deficiency suggest that the biochemical changes that occur in LGMD are not always uniform. They demonstrate that full immunohistochemical analysis of all sarcoglycan proteins is necessary for a complete assessment of a patient’s LGMD.

Another hypothesis is that specific types of disruptions in secondary structure may have different effects. The Arg91Pro mutation in β-sarcoglycan abolishes a charged amino acid and replaces it with a residue that would interrupt a β-sheet. On the other hand, the Arg91Leu mutation would not have a large effect on secondary structure, and would thus result in a milder course of disease [84,85]. Others have speculated that there may be other genes that affect disease severity [77,87], but no clear candidate has arisen. One intriguing possibility is involvement of the muscle-specific calcium-dependent neutral protease calpain 3, in which mutations have been implicated in LGMD2A [11]. This puzzling variability in LGMD presentation remains a problem for future investigation.

As noted above, sarcoglycan complex mutations lead to a reduction of α-dystroglycan [73–76]. This would result in a disruption of the dystroglycan-mediated link between the cytoskeleton and the extracellular matrix. Thus, one role of the sarcoglycan complex may be to preserve the integrity of the dystroglycan complex and thereby protect muscle cells from stress associated with muscle contraction. The precise nature of this sarcoglycan–dystroglycan interaction is currently unknown.

### Sarcoglycans and cardiomyopathy

Recently, evidence has arisen to indicate a possibly important role of the sarcoglycans in the pathogenesis of human cardiomyopathies. Cardiac manifestations are a well-known consequence of dystrophin mutations [91,92], and evidence of sarcoglycan complex disruption in the BIO 14.6 cardiomyopathic hamster, as described below, lent additional support to this hypothesis.

Cases of cardiomyopathy associated with sarcoglycan complex abnormalities have been reported. These are primarily dilated cardiomyopathies, and only in a few cases have the causative mutations been identified [93,94*,95*] (Mora M, Muntoni F, personal communication). Thus far, these patients have initially presented with diagnoses of LGMD, with eventual development of cardiac disease. However, it is possible that some patients may initially present with cardiomyopathy in the absence of skeletal muscle disease, and the presence of LGMD may not be detected. It is intriguing to speculate what fraction of the so-called ‘idiopathic’ cardiomyopathy may actually be caused by sarcoglycan complex mutations.

The identification of dilated cardiomyopathies with sarcoglycan complex disruptions fits well with a hypothesis proposed by Olson et al. [96*], who identified cardiac actin mutations in patients with idiopathic dilated cardiomyopathies. The authors drew a distinction between dilated and hypertrophic cardiomyopathy, and suggested that dilated cardiomyopathy is caused by defects of force-transmitting proteins, such as actin, and that hypertrophic cardiomyopathy is caused by defects of force-generating proteins, such as myosin and tropomyosin. This suggests that sarcoglycan complex mutations result in a reduced capacity for the DGC to transmit force to the extracellular matrix, causing the observed cases of dilated cardiomyopathy.

### Animal models

The availability of accurate animal models of muscular dystrophy can greatly facilitate the investigation of hereditary diseases. In the case of sarcoglycan-deficient LGMD, the field has benefited from a naturally occurring model, the BIO 14.6 cardiomyopathic hamster [97]. Although originally identified for its cardiac phenotype, it was known to have skeletal muscle pathology as well. Roberts et al. [74] demonstrated that the muscular dystrophy observed in this animal was caused by apparent defects in the DGC, with an immunohistologic pattern similar to that of LGMD. Others later confirmed this finding, and demonstrated the relative stability of β-dystroglycan at the sarcolemma [75,98]. Nigro et al. [99**] identified a deletion in the 5′-untranslated region of the δ-sarcoglycan gene that results in the loss of an exon specific for skeletal and cardiac muscle, and the loss of the entire
sarcoglycan complex. Subsequently, Sakamoto et al. [100] reported that the same δ-sarcoglycan deletion may cause either a hypertrophic or dilated cardiomyopathy. In addition, α-dystroglycan appears to be destabilized at the extracellular surface of muscle fibers, which is consistent with the recent finding in one human LGMD patient [73–76]. Dystrophin was also found to be less tightly associated with the sarcolemma [74].

These findings in the BIO 14.6 hamster are consistent with those from human LGMD2C–2E patients, and support one hypothesis of sarcoglycan complex function. Through its interaction with the dystroglycan complex, the sarcoglycan complex serves to stabilize the link between the cytoskeleton and extracellular matrix and protect the sarcolemma from contraction-induced damage. A mutation in any sarcoglycan protein leads to disruption of sarcoglycan complex function and to subsequent dystroglycan complex instability. Thus, the muscle fibers are more susceptible to contraction-induced damage, and muscular dystrophy results (Fig. 4) [54–56].

Mouse models of LGMD are currently under development. The first mouse knockout of a sarcoglycan gene is the α-sarcoglycan null mouse [101]. As with the BIO 14.6 hamster, the disruption of α-sarcoglycan leads to progressive skeletal muscle degeneration, which indicates that this is an accurate model of human LGMD. In the future, it is reasonable to expect the generation of null mice for the other sarcoglycan proteins. Although certain physiologic aspects might be predictable, of particular interest will be the effects that these null mutations have in nonmuscle tissues, given the ubiquitous expression of β-sarcoglycan and δ-sarcoglycan. In addition, these models provide excellent systems in which to test possible therapies, such as pharmacologic intervention or gene transfer.

**Gene therapy**

As with any hereditary disorder, there is considerable interest regarding the possible development of genetic therapy for the treatment of LGMD. The potential for Duchenne muscular dystrophy gene therapy has been extensively studied [102]. Previously, however, similar studies had not been conducted for LGMD, primarily because of uncertainty about the multiple causes of this disease.

Recently, we have demonstrated that, using an adenovirus that contains the normal δ-sarcoglycan complementary DNA, the skeletal muscle phenotype in the BIO 14.6 hamster can be corrected via direct intramuscular injection
Figure 5. δ-Sarcoglycan gene transfer in the BIO 14.6 hamster

Three-week-old BIO 14.6 hamsters, which have a deletion in the δ-sarcoglycan gene, were injected intramuscularly with an adenoviral construct encoding the human δ-sarcoglycan complementary DNA. Hamsters were subsequently examined for evidence of muscle degeneration or injected with Evans blue dye to assess membrane integrity. (a) Analysis of muscle injected with both δ-sarcoglycan adenovirus and Evans blue dye demonstrates that muscle fibers that express δ-sarcoglycan are impermeant to Evans blue, as indicated by intracellular staining of the muscle fibers. This, these fibers are less susceptible to membrane damage than uninfected muscle. (b) A higher magnification of the Evans blue result. (c) Immunofluorescence for laminin-2 and propidium iodide staining of nuclei indicates the presence of centrally located nuclei, a marker of muscle cell degeneration and regeneration. (d) Immunofluorescence for δ-sarcoglycan and propidium iodide demonstrates that the muscle fibers that express δ-sarcoglycan from the adenovirus are protected from muscle damage [102**]. Bars = 100 μm.

[103**]. With a cytomegalovirus promoter, high levels of expression can be generated from a single injection. This effect the renewed expression of all sarcoglycan proteins at the sarcolemma. Importantly, the expression of the sarcoglycan complex results in the stabilization of dystroglycan at the extracellular face. This restoration of the DGC clearly has certain functional effects. First, using Evans blue dye as a marker for sarcolemmal damage, adenoviral delivery of δ-sarcoglycan results in a dramatic reduction in membrane permeability. This demonstrates a restoration of membrane stability and integrity. Second, early administration of δ-sarco-glycan adenovirus reduces the level of central nucleation found in the transfected fibers, a hallmark of progressive muscle degeneration. This indicates that the continual cycle of muscle fiber degeneration and regeneration has been arrested (Fig. 5). Similar results have been obtained by α-sarcoglycan delivery in the α-sarcoglycan-null mouse [101].

The most remarkable finding of this recent study in the BIO 14.6 hamster [103**] is the long-term expression that was achieved. From a single injection of adenovirus into a young hamster, persistent expression from the adenovirus could be detected for as long as 6 months, with little evidence of a host immune response directed against the adenoviral construct. This may be the result of a number of factors. At an early age, the hamster may not yet be fully immunocompetent, thus allowing for the introduction of foreign genes. Also, because γ-sarcoglycan and δ-sarcoglycan share high amino acid homology, the δ-sarcoglycan protein may not be recognized as a foreign antigen. Whatever the case, the length of expression is an important consideration in the development of gene transfer therapies.

Conclusion

In the past several years, the muscular dystrophy field has seen the identification of several disease genes, including those that encode four individual sarcoglycan proteins. The number of known mutations has steadily increased, and a better understanding of the nature and course of sarcoglycan-deficient LGMD has been gained. Nevertheless, the current state of knowledge belies the work yet to be done.

Through studies with human populations, the BIO 14.6 hamster and the α-sarcoglycan knockout mouse, the role of the sarcoglycan complex in the overall stabilization of the DGC and the sarcolemma has been clarified. One exciting possibility revealed by research in this field is gene therapy for the treatment of LGMD. Unlike dystrophin, which is encoded by a very large complementary DNA, the coding region of each sarcoglycan transcript is less than 2kb. This falls well within the carrying capacity of the commonly used viral vectors that are currently under investigation. As demonstrated in the BIO 14.6 hamster, viral-mediated gene transfer can effect long-term expression with clear functional benefit. Although clinical testing in humans has not been initiated, and more study of the emerging animal models is necessary, these positive preclinical results provide hope for the development of a treatment for this debilitating disease.

Note added in press

After this review was submitted, three papers were published that have further advanced the understanding of LGMD and the sarcoglycan complex. In the September 1998 issue of Nature Genes, Liu et al. and Bashir et al. reported the identification of dysferlin as the gene mutated in LGMD2B and two allelic disorders, Miyoshi myopathy and distal myopathy with anterior tibial onset. In the September 1998 issue of the Journal of Cell Biology, Hack et al. reported the characterization of a γ-sarcoglycan knockout mouse, which developed skeletal muscle myopathy and cardiomyopathy with evidence of programmed cell death.
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References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:
* of special interest
** of outstanding interest


An excellent overview of the DGC and muscular dystrophies caused by mutations in this complex is presented. Important clinical and diagnostic considerations when evaluating patients with muscular dystrophy are highlighted.


This paper and [66] reports the characterization of a novel sarcoglycan protein that is expressed primarily in nonmuscle tissues. This protein has high homology with α-sarcoglycan, and may be a component of a nonmuscle sarcoglycan complex.

66 McNally EM, Ly CT, Kunkel LM. Human c-sarcoglycan is highly related to α-sarcoglycan (adhalin), the limb girdle muscular dystrophy 2D gene. FEBS Lett 1998; 422:27–32.


This paper demonstrates an elegant correlation between sarcoglycan expression levels and disease severity, as well as a correlation between mutation type and severity.

This is an excellent and extensive analysis of \( \alpha \)-sarcoglycan mutations.

This paper highlights the range in severity of LGMD as a result of identical mutations in the sarcoglycan complex. This is the first report of dilated cardiomyopathy with identified mutations in the sarcoglycan complex.

This is the first report of successful gene transfer for a sarcoglycanopathy. This is the first report of dilated cardiomyopathy with identified mutations in the sarcoglycan complex.