A cross section of autosomal recessive limb-girdle muscular dystrophies in 38 families

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Abstract

Limb-girdle muscular dystrophies constitute a broad range of clinical and genetic entities. We have evaluated 38 autosomal recessive limb-girdle muscular dystrophy (LGMD) families by linkage analysis for the known loci of LGMD2A-F and protein studies using immunofluorescence and western blotting of the sarcoglycan complex. One index case in each family was investigated thoroughly. The age of onset and the current ages were between 1/2 and 15 years and 6 and 36 years, respectively. The classification of families was as follows: calpainopathy 7, dysferlinopathy 3, α sarcoglycan deficiency 2, β sarcoglycan deficiency 7, γ sarcoglycan deficiency 5, δ sarcoglycan deficiency 1, and merosinopathy 2. There were two families showing an Emery-Dreifuss phenotype and nine showing no linkage to the LGMD2A-F loci, and they had preserved sarcoglycans.

γ sarcoglycan deficiency seems to be the most severe group as a whole, whereas dysferlinopathy is the mildest. Interfamilial variation was not uncommon. Cardio-myopathy was not present in any of the families. In sarcoglycan deficiencies, sarcoglycans other than the primary ones may also be considerably reduced; however, this may not be reflected in the phenotype. Many cases of primary γ sarcoglycan deficiency showed normal or only mildly abnormal δ sarcoglycan staining.


Keywords: limb-girdle muscular dystrophy; genetic linkage analysis; sarcoplemmal complex proteins

The limb-girdle muscular dystrophies (LGMD) are quite heterogeneous disorders. As a result of advances in clinical nosology with the aid of molecular genetics, different gene loci have been described. Most forms are autosomal recessive and the accepted nomenclature is LGMD2, whereas the dominant forms are designated LGMD1. Clinically they are characterised by symmetrical weakness of the pelvic, scapular, and trunk muscles, raised serum creatine kinase, and a necrotic-regenerative pattern of muscle. The symptoms usually begin during the first two decades of life, with the disease then gradually worsening, often resulting in loss of walking ability 10 to 20 years after onset.

Recently, loci for eight different diseases have been identified: 15q15 (LGMD2A),1 2 which is a muscle specific calpain-3 (CAPN3) deficiency; a dysferlinopathy on 2p6-8; the four sarcoglycanopathies in which the abnormal proteins have been identified as α sarcoglycan (SG) on 17q12 (LGMD2D)9,10 β-SG on 4q12 (LGMD2E),11 12 γ-SG on 13q12 (LGMD2C),13-15 and δ-SG on 5q33 (LGMD2F).16-19 The two most recently mapped ones do not cause disruption of the SG complex and are LGMD2G on 17q11-1220 and LGMD2H on 9q31-33.21 There is also an adult onset form of merosinopathy,22 an allelic form of a recessive condition that causes at least half of congenital muscular dystrophies of very early onset in life. Among the above described conditions, the four SG deficiencies cause disruption of the SG complex as these five proteins are closely associated in the sarcoplemma.24-26 Although the issue is not entirely clear, most recent studies suggest that caveolin-3 deficiency may show autosomal dominant or recessive inheritance.27

Although some forms are known to have a relatively benign course, such as LGMD2B,28 there is no general consensus on the other LGMD2s as the fully worked up number of affected cases are limited and the severity varies in different series. We originally reported our experience in 20 families with 33 cases that we had evaluated between January 1989 and December 1995.29 Since then, we have collected a new cohort of 41 families with 65 cases fitting the description of LGMD2, up to July 1998. Here we report the clinical, genetic, and molecular findings in 38 of these families in the light of new developments in the area. All families are Turkish. A combined approach of genetic linkage analysis with protein data comprising immunofluorescence (IF) and western blotting were used to classify families into further groups. We have mutational data on three of these families and two of them were included in our previous series.29 We intentionally included them here for the reasons stated below.

Material and methods

PATIENTS

Hacettepe University Children’s Hospital in Ankara is a major referral centre for neuromuscular disorders in Turkey. Our selection criteria, which we have modified from our previous publication,29 were as follows: (1) a pedigree clearly compatible with autosomal recessive inheritance, (2) onset after the child had
started to walk, (3) progression of muscle weakness of varying severity showing a limb-girdle distribution with sparing of facial and ocular muscles, (4) a muscle biopsy typically compatible with a muscular dystrophy, and (5) normal dystrophin and emerin immunohistochemistry in the biopsies.

Although it may be difficult to classify the severity of the disease, as the time between the onset of symptoms and the rate of evolution may be short at times, the following parameters are chosen for practical purposes for grading the functional stage of dystrophy in a mainly paediatric setting: (1) severe, if onset was in childhood and the disability was similar to Duchenne muscular dystrophy (DMD), (2) intermediate, if onset was in childhood and the progression or disability was like Becker muscular dystrophy (BMD), (3) moderate, if onset was in adulthood and the patient showed physical disability of any grade, and (4) benign, if onset was in adulthood and the patient did not have any disability (able to run freely, but some weakness, less than grade I). The classification of DMD and BMD was taken from Dubowitz, that is, a child who becomes unable to walk before the age of 13 is registered as DMD-like, and one that is still ambulant after the age of 16 is registered as BMD-like.

There were 18 multiplex families. Consanguinity was present in 39 of 41 families. The study was carried out in 38 families in whom genetic linkage analysis and protein data showed correlation. Twenty of the 38 index cases were girls. Only one index case was studied clinically per family. The age at onset of cases was at least five times higher than normal.

Duration of follow up was between 1 and 11 years.

CARDIAC EVALUATION
Chest x-ray and routine EKG recordings were obtained twice yearly. Cardiac echograms, which were performed in 33 index cases, were normal.

MUSCLE BIOPSY
Muscle biopsies were performed after informed consent using standard open biopsy techniques under local anaesthesia by two of us (ED and HT). One family refused muscle biopsy, but they gave consent for DNA studies. Samples were snap frozen in isopentane, cooled, and stored in liquid nitrogen until processed. Frozen blocks were also used for western blotting.

Six serial micron sections cut using a cryostat were stained for routine histology by haematoxylin-eosin and modified Gomori-trichrome along with a battery of histochemical reactions. IF studies were done for the following: spectrin (NCL-SPEC1®), dystrophin (NCL-DYS1®, DYS2® and DYS3®), alpha-SG (NCL-50DAG®), beta-SG (NCL-43DAG®), gamma-SG (NCL-35DAG®), delta-SG (NCL-35DAG®), laminin α2 chain (NCL-MEROSIN®), and emerin (NCL-EMERIN®).

IMMUNOBLOTS
Immunoblot analyses were performed in 37 patients as described by Piccolo et al and also by using a multiplex system of different antibodies (for example, Dys2, α, and γ antibodies are used for hybridisation of one membrane whereas Dys1, β, and δ antibodies are used for the hybridisation of the other in the same patient) as described by Anderson and Davison.

The primary antibodies were the same for immunofluorescence. Additional β and γ-SG antibodies were kindly provided by K Campbell, Iowa, USA.

GENOTYPING, LINKAGE STUDIES, AND MUTATIONS
DNA was obtained from peripheral blood after signed consent of the individual family members. Highly polymorphic markers of chromosomes 2p13-p16, 4q12, 5q33-q34, 13q12, 15q15.1-q15.3, and 17q12-q21.33 were used for analysing the 38 LGMD2 families. The fluorescent labelled markers for LGMD2A, LGMD2B, LGMD2C, LGMD2D, LGMD2E, and LGMD2F patients were arranged in three different groups (2A with 2B, 2C with 2D, 2E with 2F), so that all of the markers could be tested together in a multiplex system. All of the 41 families, except two, were consanguineous and linkage was ascertained by homozygosity by descent (HBD). In inbred populations such as ours, this method has been proven to be very fruitful; however, in the absence of consanguinity the same yield may not be obtained. In three of the families linkage analysis was not sufficient to identify the chromosome responsible. Thus, these families were not included in this paper. The closest markers used for each locus were as follows. Markers for LGMD2A: 070xd7, 806G4G10-d, 854f9b4, 944b11-d, 265xf9-d; markers for LGMD2B: a343xe9, 203xc3, a205zc5, a296xc5; markers for LGMD2C: D13S232, a217ylb5, 351xd9-d, c021xe1; markers for LGMD2D: CA-ADL, a351we1, 234td2, 269xb1-d, 269xd1; markers for LGMD2E: 189xa5, 274xb9, CA12T, b535yh9; and markers for LGMD2F: 336xe9, 329f5, 191xd8-t. Mutations of γ and δ sarcoglycans have been published and submitted elsewhere (Dinçer et al, submitted).

Results
The vast majority of our families were closely consanguineous. We put our LGMD2 families following the immunohistochemistry, western blotting, and linkage analysis data into alphabetical order, that is, from LGMD2A to LGMD2F, and taking into consideration the physical stigmata and protein studies of the Emery-Dreifuss phenotype. As we have not genotyped our families for the G and H loci yet, we have classified the rest as “others”. The SG complex was preserved in the calpainopathy, dysferlinopathy, merosinopathy, Emery-Dreifuss phenotype, and “other” groups. A summary of the clinical features of our series is

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presented in table 1. Cardiomyopathy was not found in any of our cases. In general, interfamilial variability of symptoms was a common finding in most groups.

GROUP 1: CALPAINOPATHY
There were seven index cases in this group, with ages varying between 11 and 37. They all have an intermediate to moderate clinical course so far. There were three patients with a delayed walking age of 1 1⁄2 and 2 years. The 37 year old patient comes from a large pedigree where one distant cousin is homozygously affected. Interestingly, this patient has a heterozygous haplotype (data not shown), with mild symptoms and a raised CK of 1400 U/l. Scapular winging was present in five cases and calf hypertrophy was seen to a mild degree in two of the older patients, but generally it was of atrophic type with the hamstrings being more wasted.

GROUP 2: DYSFERLINOPATHY
There were three families in this group. The patients' ages are between 13 and 21. One patient had walked late at the age of 3 years. This patient also has ataxia telangiectasia. One of them shows distal features such as muscle wasting, fitting into the Miyoshi phenotype. All cases typically have moderate to benign courses. Mild calf hypertrophy was present in one case.

GROUP 3: SARCOGLYCANOPATHY
This group could be divided into four subgroups.

<table>
<thead>
<tr>
<th>α-sarcoglycan deficiency</th>
</tr>
</thead>
<tbody>
<tr>
<td>11 14 (11) F − 1 − −</td>
</tr>
<tr>
<td>12 18 (6) M − 1 − +</td>
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<tr>
<td>β-sarcoglycan deficiency</td>
</tr>
<tr>
<td>13 8 (5) F − 1 + +</td>
</tr>
<tr>
<td>14 23 (14) F + 1 + +</td>
</tr>
<tr>
<td>15 29 (14) F + 1 + +</td>
</tr>
<tr>
<td>16 8 (2) F − 1 1⁄2 − +</td>
</tr>
<tr>
<td>17 13 (6) M + 1 − −</td>
</tr>
<tr>
<td>γ-sarcoglycan deficiency</td>
</tr>
<tr>
<td>18 19 (13) M − 1 + +</td>
</tr>
<tr>
<td>19 12 (2) F − 1 − −</td>
</tr>
<tr>
<td>δ-sarcoglycan deficiency</td>
</tr>
<tr>
<td>20 6 (3) M − 1 − +</td>
</tr>
<tr>
<td>21 10 (3) M − 3 − −</td>
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<tr>
<td>22 11 (7) M + 1 − −</td>
</tr>
<tr>
<td>23† 20 (7) F − 1 1⁄2 − +</td>
</tr>
<tr>
<td>24† 14 (6) F + 1 1⁄2 − +</td>
</tr>
<tr>
<td>Emery-Dreifuss phenotype</td>
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<tr>
<td>25† 14 (8) F − 1 1⁄2 − −</td>
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<tr>
<td>Others</td>
</tr>
<tr>
<td>26 8 (1 1⁄2) F + 1 − −</td>
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<tr>
<td>27 8 (2) F − 1 1⁄2 − −</td>
</tr>
<tr>
<td>28 12 (3) F − 2 − −</td>
</tr>
<tr>
<td>29 17 (10) M + 1 − −</td>
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<tr>
<td>30 20 (6) M + 3 − +</td>
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<tr>
<td>31 36 (17) M − 1 − +</td>
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<tr>
<td>32 17 (2) M − 1 − −</td>
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<tr>
<td>33 17 (5) M − 5 − −</td>
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<td>34 20 (6) M + 2 − −</td>
</tr>
<tr>
<td>35 26 (15) M + 1 1⁄2 − −</td>
</tr>
<tr>
<td>36 8 (2) M + 1 1⁄2 − −</td>
</tr>
<tr>
<td>37 18 (6) F + 2 1⁄2 − +</td>
</tr>
<tr>
<td>38 14 (7) F − 1 1⁄2 + +</td>
</tr>
</tbody>
</table>

Scapular w: scapular winging.
*Also has ataxia telangiectasia.
†Mutation studies completed.

The ages of two patients belonging to this group are 10 and 14 years. The 10 year old boy with an onset of 6 years has become unable to walk within 4 years, thus presenting a severe DMD-like picture that includes pseudohypertrophy of the calves and thighs. The other patient has an intermediate to moderate course with unremarkable features. Protein data in both cases showed reduction of the other three SGs as well as the primary one, with the severe case having more reduction of α-SG (table 2).
**Table 2** Properties of sarcoglycans in sarcoglycanopathies

<table>
<thead>
<tr>
<th>Case</th>
<th>α-SG</th>
<th>β-SG</th>
<th>γ-SG</th>
<th>δ-SG</th>
<th>Age, clinical stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>11</td>
<td>++</td>
<td>+++</td>
<td>+++</td>
<td>++</td>
<td>14, I</td>
</tr>
<tr>
<td>12</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>0</td>
<td>10, VI</td>
</tr>
<tr>
<td>13</td>
<td>++</td>
<td>++</td>
<td>+</td>
<td>+++</td>
<td>13, II</td>
</tr>
<tr>
<td>14</td>
<td>+++</td>
<td>N.D.</td>
<td>++</td>
<td>N.D.</td>
<td>24, II</td>
</tr>
<tr>
<td>15</td>
<td>N.D.</td>
<td>N.D.</td>
<td>N.D.</td>
<td>N.D.</td>
<td>29, II</td>
</tr>
<tr>
<td>16</td>
<td>++</td>
<td>0</td>
<td>+++</td>
<td>++</td>
<td>8, I</td>
</tr>
<tr>
<td>17</td>
<td>++</td>
<td>+</td>
<td>+++</td>
<td>+</td>
<td>13, II</td>
</tr>
<tr>
<td>18</td>
<td>+++</td>
<td>+++</td>
<td>+</td>
<td>++</td>
<td>10, II</td>
</tr>
<tr>
<td>19</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
<td>++</td>
<td>12, I</td>
</tr>
</tbody>
</table>

- = mildly reduced, ++ = moderately reduced, +++ = severely reduced, 0 = absent.
* = Mutation studies completed.

Show intermediate to moderate clinical courses. The oldest patient in this group, a 29 year old female, is only moderately affected and has a 4 year old unaffected daughter (fig 1). Her evolution is the mildest in this particular family, but other affected members of the family were more severe, again to a varying degree. Scapular winging and prominent calves were present in four and six cases, respectively. Again, all SGs showed various degrees of reduction in each individual case with β-SG being severely reduced or zero.

**γ-SG deficiency**

This group shows a rapidly progressive evolution. Among the five patients with ages between 6 and 20 years, there are two cases with intermediate and three cases with severe evolution. One case started walking at 3½ years and in two others walking was delayed at 1½ years. Four patients have calf hypertrophy and none has scapular weakness. Protein studies showed reduction of α, β, and γ SGs with γ-SG being the most degraded one; however, δ-SG was preserved or mildly reduced in these patients (table 2). This was true for both linkage (n=3) and mutation proven (n=2) cases.

We intentionally took the latter cases in this series to “double-check” this correlation. Both patients had a homozygous 923-924 del TG mutation.

**δ-SG deficiency**

We have one patient in this group. She definitely has a severe DMD-like course with onset at the age of 8 and then becoming wheelchair bound by the age of 12. All her SGs are severely reduced. There is no cardiomyopathy. Mutation data show that she has a stop codon in exon 3 (Dinçer et al, submitted).

**Merosinopathy**

The two girls in this group aged 8 and 6 years had onset at 1 year and 18 months, respectively. Both cases walked before 18 months of age. They are both ambulant with mild motor handicap, so are classified as intermediate to moderate. We have been following them for six and two years, respectively, and there has been no worsening of symptoms. Laminin α2 chain is mildly reduced in IF studies against the 80 kDa portion of the protein, the classical antibody. They both have typical white matter changes on cranial MRI scans confirming merosin deficiency.

**Others**

**Emery-Dreifuss phenotype**

Both families presented with somewhat distal features, such as Achilles tendon shortening, elbow contractures, and rigid spine to a mild degree.

Immunostaining against emerin antibodies was normal. One of the index cases was a 12 year old girl.

**Remaining cases**

We have a total of nine families with typical proximal weakness showing a limb-girdle distribution for which we could not find the locus responsible.

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**Figure 1** Pedigree of a family with LGMD2E (family 15).
In four families linkage by homozygosity by descent was to the LGMD2F region. We further screened the gene and did not find any mutations. All sarcoglycans were preserved in all four, unlike the case in β sarcoglycan deficiency. This suggests linkage by chance because of smaller family sizes. Three patients, despite relatively early onsets of 2 and 5 1/2 years, are very mild clinically and could be considered as intermediate to moderate. The oldest case of our series is now 36 years old and belongs to this latter group. This case has been reported twice before elsewhere.29 36 He is the only one in our series with a quite benign course.

The remainder are five families with the index cases being between 8 and 26 years old. None of them showed any distal features. Linkage analysis excluded all the known loci from LGMD2A to F.

**Discussion**

We have identified several subgroups in our country where consanguineous marriages are frequent.13 Our aim was not to make a phenotype/genotype correlation, but to give a cross section of different subgroups within LGMD2.

The prevalence of LGMD has been estimated to be 20-40 per million.38 However, this figure varies in different series. In isolated populations such as Réunion, it has been found to be 48 per million19 and in the Basque country the figure is as high as 69 per million.20 The high rate of inbreeding and the number of multiplex families (n=18) may result in the relatively high number of cases in our setting.

So far, with our previous publication,29 we have identified several subgroups in our families from the Réunion Islands, about 50% of which were not linked. In our current experience, Urtasun et al11 the clinical onset was at 7.6 years (range 4 to 12) and loss of walking at 26 years (range 12 to 38 years), with marked interfamilial variability. All seven cases were at the LGMD2F region. We have also experienced the same in our cases from previous and current series. This entity can even have a true onset after puberty. One of our cases had somewhat benign courses, all our cases had greatly increased CK levels, 23-40 times higher than normal values.

**SARCOCYLANopathies**

We know from mutation analysis that missense mutations are usually associated with a milder phenotype while truncating mutations tend to produce a more severe course.10 11 13 However, clear exceptions to this generalisation have been seen.46–48

**α-SG DEFICIENCY**

Primary α-SG deficiency is clinically heterogeneous, the severity of the disease varies strikingly, and correlates in part with the type of mutation and the amount of residual protein.49 In our two cases, the severe one who lost ambulation within four years after onset at 6 years of age had zero α-SG in the protein studies, whereas the milder case had only reduced levels of protein.

**β-SG DEFICIENCY**

Patients belonging to this group may also be severe or mild. Calf hypertrophy may be present. There are Amish patients who are still ambulant in the fifth decade. In the original Amish series by Lim et al,11 the clinical onset was at 7.6 years (range 4 to 12) and loss of walking at 26 years (range 12 to 38 years), with marked interfamilial variability. All seven cases in our group have either intermediate or moderate clinical courses so far. On the other hand, the only case from our previous report had a severe outcome. Onset was at 12 years and she lost ambulation by the age of 20.29 As a whole, all SGs show substantial reductions in the biopsies. It is interesting to note that, despite SG loss, patients could have mild to moderate clinical courses at least to their current ages, in our experience the oldest being 24.
γ-SG DEFICIENCY
This probably constitutes the most severe of all the sarcoglycan deficiencies. In this group, the majority of patients were severely affected. The two intermediate of our cases were younger than 11 years of age, so their prognosis may also be severe in due course. γ-SG was severely reduced or zero as has been well documented.45 46 In the series of Vainzof et al47 there was a complete absence of γ-SG.
Interestingly, in their cases, δ-SG seems to be the most preserved, as detected in our series, probably indicating that γ-SG is loosely associated with δ-SG in the sarcolemmal membrane. Thus, the retention of some of the SG components should not be considered prognostic for a milder phenotype.

δ-SG DEFICIENCY
The patient has a stop codon mutation, has complete absence of the SG complex, and presents with a severe phenotype. All the reported cases within this group similarly have severe evolution.18 45

MEROSINOPATHY
We previously described the original patient with late onset merosin deficiency.22 Abnormalities of merosin (laminin α2 chain) normally result in a very severe congenital onset muscular dystrophy, but its allelic variant, the 300 kDa portion of the laminin α2 chain is missing or reduced.23 The two patients we have had walked at 1 and 1 1⁄2 years, respectively. This is far beyond the clinical description of classical merosin deficiency, in which patients must have symptoms before the age of 6 months. Also, they both had typical MRI changes in the white matter. These patients with merosin deficiency once again remind us that this latter condition should also be included in the differential diagnosis of LGMD2.

EMERY-DREIFUSS PHENOTYPE
Typical EMD is an X linked disorder.50 However, there is also an autosomal dominant form.51 This is located at the locus described in three families identified as having autosomal dominant limb-girdle muscular dystrophy with cardiac involvement.52 Also, Bethlem myopathy may be a mimicking condition.53 The typical clinical stigmata are of distal findings such as contracture of the elbows and Achilles tendons with rigidity of the neck muscles in some cases. In the X linked form patients develop cardio-myopathy after their teens. With the presence of consanguinity, our two families suggest autosomal recessive inheritance. However, further analyses are needed.

OTHERS
There are occasional LGMD families where no linkage to any of the known chromosomal loci has been found. We have nine families with this condition except that linkage studies for the most recently described loci of LGMD2G and H have not been performed. They all have preserved SGs and the classical features of proximal and progressive weakness. It is unlikely that any of these families could be linked to the LGMD2G locus, as this condition is mostly distal.28 So far, LGMD2H has been reported only in Hutterites in Manitoba and presents with a relatively mild muscular dystrophy.22 As caveolin-3 deficiency may be autosomal recessive in some families, this must be checked in our remaining series.27
So far, our genetic linkage analysis and protein data have shown good correlation, that is, all our unlinked families have normal sarcoglycans, and all cases with reduced sarcoglycan were linked to a specific sarcoglycan locus. Mutation studies are under way.

To summarise our findings, there is extreme heterogeneity in the clinical presentation and some patients have delayed onset of walking. Interfamilial variation is not uncommon. Scapular winging and selective wasting of the hamstrings is peculiar to calpainopathy. All cases of dysferlinopathy have a milder evolution. Calpainopathy is a cardinal feature of sarcoglycan deficiencies. γ-SG deficiency seems to be the most severe group. Cardiomyopathy was not encountered in our series. As far as the protein studies are concerned, this may help to distinguish the gene responsible. At the δ-SG locus all SGs are reduced; however, in the clinic not all patients are severe. In γ-SG deficiency, γ-SG is always severely reduced or zero at the locus, but δ-SG is normal or only mildly abnormal. Finally δ-sarcoglycan deficiency causes almost complete disarray of the complex.

We are grateful to our muscular dystrophy families who have fully participated in this project. This study was partially funded by a grant from the TUBITAK (STAG-1774). We would like to thank the Association Française contre les Myopathies (AFM), France for continuous support. We thank Carsten Bönneman, University of Göttingen who did the mutation analysis in the γ- and δ-sarcoglycan genes. We would like to acknowledge Genechip, France for their skilful technical assistance. The International Atomic Energy Agency (IAEA) has also contributed to the project.

Autosomal recessive limb-girdle muscular dystrophies


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