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ORIGINAL COMMUNICATION

Diagnostic value of muscle MRI in differentiating LGMD2I from other LGMDs

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Abstract Mutations in the fukutin-related protein (FKRP) have recently been demonstrated to cause limb girdle muscular dystrophy type 2I (LGMD2I), one of the most common forms of the autosomal recessive LGMDs in Europe. We performed a systematic clinical and muscle MRI assessment in 6 LGMD2I patients and compared these findings with those of 14 patients with genetically confirmed diagnosis of other forms of autosomal recessive LGMDs or dystrophinopathies. All LGMD2I patients had a characteristic clinical phenotype with predominant weakness of hip flexion and adduction, knee flexion and ankle dorsiflexion. These findings were also mirrored on MRI of the lower extremities which demonstrated marked signal changes in the adductor muscles, the posterior thigh and posterior calf muscles. This characteristic clinical and MRI phenotype was also seen in LGMD2A. However, in LGMD2A there was a selective involvement of the medial gastrocnemius and soleus muscle in the lower legs which was not seen in LGMD2I. The pattern in LGMD2A and LGMD2I were clearly different from the one seen in alpha-sarcoglycanopathy and dystrophinopathy type Becker which showed marked signal abnormalities in the anterior thigh muscles. Our results indicate that muscular MRI is a powerful tool for differentiating LGMD2I from other forms of autosomal recessive LGMDs and dystrophinopathies.

Key words FKRP · limb-girdle muscular dystrophy · LGMD2I · clinical phenotype · MRI

Introduction

α-dystroglycan is a heavily glycosylated peripheral membrane component of the dystrophin-associated glycoprotein complex (DAG) that serves as a linker to the extracellular basal lamina, whereas β-dystroglycan is a transmembrane protein that interacts with dystrophin intracellularly. Dystroglycan therefore plays an essential role in linking the intracellular cytoskeleton to components of the extracellular matrix. Disruption of this linkage is associated with several forms of muscular dystrophy (Michele et al. 2002). Recently, a novel gene encoding a putative glycosyltransferase, fukutin-related

protein (FKRP), was found to be responsible for both a novel form of congenital muscular dystrophy (MDC1C) and for a form of limb girdle muscular dystrophy (LGMD2I) (Brockington et al. 2001a, b; Mercuri et al. 2003; Poppe et al. 2003). In a recent study, we noticed LGMD2I to be very common in adult LGMD patients in Germany, within the range or even exceeding the frequency of LGMD2A (calpainopathies), LGMD2B (dysferlinopathies) and LGMD2C-F (sarcoglycanopathies) (Walter et al. 2004). However, there are only two studies of the clinical phenotype of LGMD2I available (Mercuri et al. 2003; Poppe et al. 2003). A systematic muscle MRI analysis in LGMD2I in comparison with other muscular dystrophies has not been published so far. To further delineate the phenotype of patients harbouring FKRP mutations, and with special emphasis on the selectivity of muscular involvement, we analysed the clinical and muscle MRI pattern in six genetically confirmed LGMD2I patients and compared these findings with those in other genetically confirmed LGMDs and muscular dystrophy type Becker.

Methods

Patients

Six patients aged 32–48 years from 4 different families with a genetically confirmed diagnosis of LGMD2I were included in this study. Five patients were homozygous for the most common single point mutation (826C > A) leading to an Leu276Ile amino acid exchange, whereas one patient (patient 6) was compound heterozygous with 826C > A (276L > I) and 341C > G (496R > X) mutations. Clinical, genetic and muscle biopsy findings of all patients with exception of patient 3, a symptomless sibling of patient 1 and 2, have been described in detail (Walter et al. 2004). Muscular strength was assessed in all patients according to MRC grade as described (Fischer et al. 2003b). In analogy to a recent publication on the clinical phenotype of LGMD2A, we further characterized the clinical phenotype in terms of balance of forces around a particular joint and compared the relative strength of flexors and extensors, adductors and abductors of the proximal and distal upper and lower limbs as suggested previously (Pollitt et al. 2001).

Further, we studied 14 patients with other forms of genetically confirmed diagnosis of LGMD represented as follows: LGMD 2A, n = 5 (patient 7: Ex4:550delA and Ex16:1865–1875del; the second mutation is novel and will be described elsewhere (Nigro et al. in preparation); patient 8: Ex4:598–612del, second mutation not yet found; patient 9: Ex5:801 + 1G > A and Ex14:1746–20C > G; patient 10: Ex5:759–761del and Ex14:1746–20C > G; patient 11: homozygous Ex11:1469G > A); LGMD 2B, n = 5; patient 12: 3208G > T and 3819–3820delTT; patient 13: Ex 30:3570InsCGGAGG and Ex 51:6101 A > C; patient 14 and 15: Ex9:1237InsA (D327X) and Ex30:3570InsCGGAGG for details see (Walter et al., 2003); patient 16: Ex4:638C > T and Ex44:5245G > C and 5249del); LGMD 2D, n = 2 (patient 17: homozygous 371T > C; for details see (Fischer et al. 2003a); patient 18: Ex3: 229C > T and Ex6: 739G > A) and dystrophinopathy type Becker, n = 2 (in-frame-deletion of exon 48; in-frame-deletion of exon 3 and 4). Informed consent in writing for genetic testing and MRI examination was obtained from all individuals included in this study.

Muscle MRI

Muscle MRI was performed on a 1.5-Tesla scanner (Gyroscan NT-Intera, Philips, Best, The Netherlands) using standardized conditions as proposed by Mercuri and colleagues (Mercuri et al. 2002a, b). Our protocol included transverse T1W spin echo (TR = 450 ms, TE = 20, matrix 256 x 256, FOV = 40 cm) and T2W SPIR sequences (TR = 2600 ms, TE = 80, matrix 256 x 256, FOV = 40 cm, slice thickness = 5 mm). Ten five mm thick transverse slices were obtained from each pelvis, thighs and lower legs. The MRI scans were seen by a neuroradiologist and a neurologist, blinded to clinical and genetic data. No abnormal signal changes on the T2W SPIR sequences indicating a possible inflammatory process were observed. For evaluation of muscular dystrophies the scans were examined for normal and abnormal muscle bulk (atrophy/hypertrophy) and for abnormal signal intensity on T1 weighted images. Each muscle group was staged according to the degree of degeneration as previously suggested (Mercuri et al. 2002a, b):

Stage 0: normal appearance.
Stage 1: early moth-eaten appearance with scattered small areas of increased signal.
Stage 2a: late moth-eaten appearance with numerous discrete areas of increased signal with beginning confluence, comprising less than 30 % of the volume of the individual muscle.
Stage 2b: late moth-eaten appearance with numerous discrete areas of increased signal with beginning confluence, comprising 30–60 % of the volume of the individual muscle.
Stage 3: washed-out appearance, fuzzy appearance due to confluent areas of increased signal.
Stage 4: end stage appearance, muscle replaced by increased density of connective tissue and fat, with only a rim of fascia and neurovascular tissue distinguishable.

The following muscles were evaluated:
pelvis: gluteus maximus, gluteus medius
thigh: vastus medialis, vastus intermedius and lateralis, gracilis, adductor muscles, semimembranosus, semitendinosus, biceps femoris
lower legs: tibialis anterior, peroneal longus, soleus, gastrocnemius

Results

Selective muscular involvement in LGMD2I

Detailed clinical information of each patient is given in Table 1. The clinical phenotypes of patient 1 and 2 are illustrated in Fig. 1. Upper limbs and shoulder girdle: In five patients, shoulder adduction was weaker than abduction and internal rotation was weaker than external rotation. Furthermore, five patients showed a weaker elbow flexion than elbow extension. Only one patient had distal involvement with slight weakness of hand extension. Scapular winging was observed in two patients (Fig. 1C). Lower limbs and pelvic girdle: In five patients, hip flexion was weaker than extension, whereas one patient had equal weakness of hip flexion and extension. Similarly, hip adduction was weaker than abduction in five patients and equal in one. Knee flexion was weaker than extension in all six patients. In the lower legs ankle dorsiflexion was weaker than ankle plantarflexion in four patients and one patient had equal weakness of ankle dorsiflexion and plantarflexion, whereas one patient

Table 1 Patient data and distribution of clinical weakness in the LGMD2I patients according to the MRC grade

Patient	Diagnosis	Patient data				Clinical weakness					
		sex	onset	age	duration	shoulder	elbow	hand	hip	knee	ankle
1 (1)*	LGMD 2I	f	5	40	35	Ad 2, Ab 3, IR 3, ER 4	F 3, E 4+	E 4+	F 3, E 4–, Ad 3, Ab 3	F 4–, E 4+	DF 4
2 (3)*	LGMD 2I	m	10	35	25	Ad 4–, Ab 4+, IR 3, ER 4+	F 4+	–	F 3, E 4–, Ad 3, Ab 4	F 3, E 4	DF 4+
3	LGMD 2I	m	32	32	0	–	–	–	F 4+, Ad 4+	F 4+	–
4 (6)*	LGMD 2I	f	15	46	31	Ad 4, IR 4+	F 4+	–	F 3, E 4, Ad 3, Ab 4	F 4–	DF 4+
5 (13)*	LGMD 2I	f	23	48	25	Ad 4–, IR 4+	F 4+	–	F 3, E 4–, Ad 3	F 4+	DF 4
6 (18)*	LGMD 2I	m	15	40	25	Ad 4, IR 4+	F 4, E 4+	–	F 3, E 3, Ad 1, Ab 3	F 2, E 3	DF 4, PF 4
7	LGMD 2A	m	10	22	12	Ad 3, Ab 4, IR 3, ER 4	F 4+	–	F 2, E 2–3, Ad 2, Ab 2	F 2, E 4	DF 3, PF 4
8	LGMD 2A	m	10	18	8	Ad 4, Ab 4+, IR 4, ER 4+	F 4	–	F 3, E 4+, Ad 4–, Ab 4+	F 4, E 4+	DF 4+
9	LGMD 2A	w	13	38	15	Ad 4–, Ab 4, IR 4+, ER 4	F 3+	E 4+	F 4–, E 4, Ad 4–, Ab 4	F 3, E 4	DF 4+
10	LGMD 2A	w	37	57	20	IR 4, ER 4+	–	–	F 4+, E 4	F 4	DF 4+
11	LGMD 2A	w	28	43	15	Ad 4, Ab 4–, IR 4, ER 4+	–	–	F 3, E 2+, Ad 3, Ab 4+	F 3, E 4	DF 4+
12	LGMD 2B	m	17	30	13	–	F 3	F 4	F 3, E 4–, Ad 3, Ab 4–	F 2, E 3	DF 1, PF 2
13	LGMD 2B	m	14	35	21	Ab 5–, IR 5–, ER 5–	F 4,	–	F 3–, E 3+, Ad 3, Ab 3	F 2, E 2	DF 3–, PF 2+
14	LGMD2B	f	19	27	8	Ad 4, Ab 4, IR 4, ER 4	F 4–, E 5–	–	F 3, E 3–, Ad 3, Ab 3	F 3, E 4–	DF 3, PF 3–
15	LGMD2B	f	20	30	10	Ab 5–	–	–	F4+, E 5–, Ad 5–, Ab 5–	F 4+, E 4	DF 4–, PF 3+
16	LGMD2B	f	24	39	15	Ad 5–, Ab 5–	F 4+	–	F 4+, E 4, Ad 4, Ab 4	F 5–, E 4+	DF 2, PF 2
17	LGMD 2D	f	2	12	10	Ad 4–, Ab 4–, IR 3	F 4	–	F 3, E 3, Ad 3, Ab 3	F 4, E 3	DF 4+
28	LMGD 2D	m	14	60	46	Ad 3+, Ab 3+, IR 3, ER 3	F 4	–	F 3, E 4, Ad 4, Ab 4	F 4, E 3	DF 2, PF 4–
19	Becker	m	20	37	17	–	F 4+	–	F 3, Ad 4, Ab 3	F 3, E 4	–
20	Becker	m	22	36	14	–	–	–	Ab 4	E 4	DF 4+

Age age at examination; *Ab* abduction; *Ad* adduction; *DF* dorsiflexion; *E* extension; *ER* external rotation; *F* flexion; *IR* internal rotation; *PF* plantarflexion. * identification number as used in reference [Walter et al. 2003]

had no distal weakness. Calf hypertrophy was observed in five patients.

None of our patients had facial weakness, tongue hypertrophy, dysphagia, contractures or signs of muscular hyperirritability. One individual (patient 1) had a mildly reduced forced vital capacity and one patient (patient 2) had a mildly reduced cardiac ejection fraction. CK levels were elevated in all patients (range 350–1922 U/L, normal < 190 U/l).

Muscle MRI findings in LGMD 2I

Detailed information on the MRI scores in each patient is given in Table 2. MRI findings of LGMD2I patients with a mild, moderate and severe clinical phenotype are illustrated in Fig. 2. Pelvis muscles (Fig. 2A, D, G): Six patients showed moderate to severe hyperintense signal abnormalities of the gluteus maximus muscle on T1 weighted images. The gluteus medius muscle showed mild to moderate involvement in four and severe in two patients. Thigh (Fig. 2B, E, H): In all six patients muscles of the posterior compartment (adductor muscles, semimembranosus and biceps femoris) showed marked hyperintense signal changes. In one patient with a mild clinical phenotype (Fig. 2B), only the adductor muscles and the biceps femoris muscle were severely affected, whereas the semimembranosus and semitendinosus were relatively spared. In contrast to the hamstring muscles, in the anterior thigh compartment a less severe involvement with only mild to moderate hyperintense signal changes was observed in five of six patients. In this context it is noteworthy that the vastus medialis and rectus femoris muscles were relatively spared compared with the vastus lateralis and vastus intermedius muscles in four patients with a milder clinical phenotype. Only the patient with a particularly severe clinical phenotype had marked signal changes in the anterior thigh compartment muscles (Fig. 2H). Five patients showed hypertrophy of the gracilis muscle. Lower legs (Fig. 2C, F, I): Five patients showed mild to moderate diffuse inhomogeneity and only one patient (Fig. 2h) severe hyperintense signal changes of the medial head of the gastrocnemius muscle, which exceeded the involvement of the lateral head. One half of the patients had mild and the other half of the patients had moderate changes in the soleus muscle. Three patients had moderate signal changes in the peroneal longus muscle, while two patients showed mild and one patient moderate changes in the tibial anterior muscle.

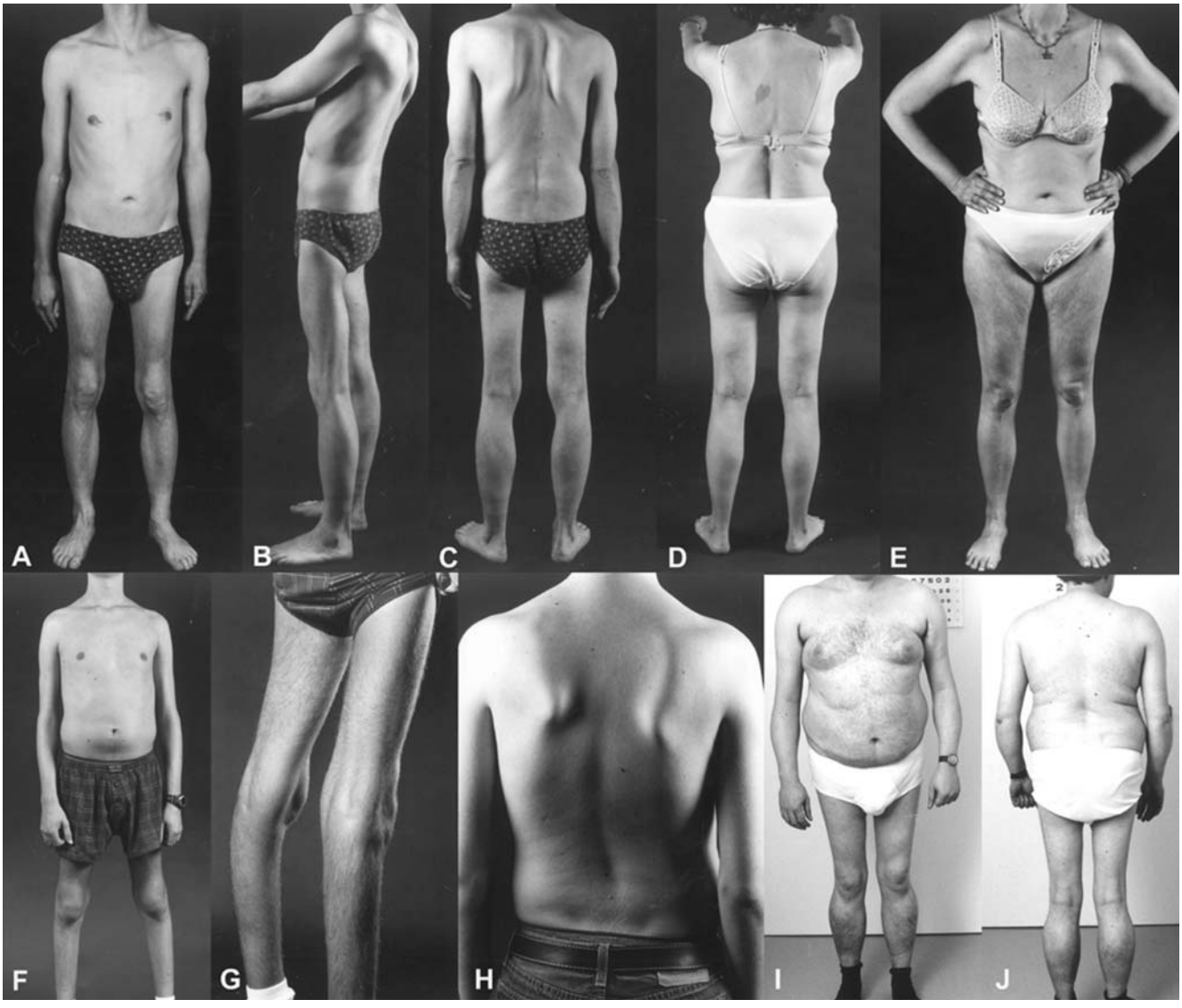

Fig. 1 Clinical phenotype of two siblings with LGMD2I: patient 2 (**A, B, C**) displayed scapular winging, severe atrophy of the gluteus maximus and the posterior thigh muscles, whereas his sister (patient 1; **D, E**) with a similar degree of clinical severity, had no weakness of the scapular fixator muscles. Clinical phenotype of a patient with LGMD2A with severe atrophy of the posterior calf muscles and scapular winging (**F, G, H**), and the phenotype of a patient with Becker's disease (**I, J**) with marked calf hypertrophy but no scapular winging

Clinical and MRI findings in disease controls

Calpainopathy

The clinical pattern of muscular weakness in five patients with LGMD2A was similar to the one observed in the patients with LGMD2I. They presented with prominent weakness of shoulder adduction, internal rotation hip, flexion and adduction, knee flexion and ankle dorsiflexion. However, whereas five of our LGMD2I had calf hypertrophy and only two presented with scapular winging all five LGMD2A patients had marked calf atrophy and scapular winging. Prominent atrophy of the gluteus maximus and posterior calf muscles was seen in three patients.

MRI findings of LGMD2A patients with a mild, moderate and severe clinical phenotype are illustrated in Fig. 3. Pelvis muscles: three LGMD2A patients had moderate to severe hyperintense signal changes and severe atrophy of the gluteus maximus muscle, whereas the other patients showed only signal changes in these muscles. All five LGMD2A patients had severe signal changes in the gluteus medius muscle (Fig. 3A, D, G). Thigh: similar to LGMD2I all patients displayed severe signal abnormalities in all hamstring muscles and adductor muscles, while the quadriceps muscle was much

Table 2 Details of MRI scores in the reported patients

Patient	Diagnosis	GMa	GMe	VL/VIM	VM	G	AM	SM	BF	TA	PL	S	Gc
1	LGMD 2I	3	2a	3	1	H	3	3	3	0	0	2a	2a
2	LGMD 2I	3	2b	2b	0	H	3	3	3	1	1	2a	2b
3	LGMD 2I	2b	1	2a	0	H	2b	2a	3	0	0	1	1
4	LGMD 2I	2b	2a	1	0	H	3	3	3	1	1	2b	2b
5	LGMD 2I	3	3	2b	2b	H	3	3	3	1	0	1	2a
6	LGMD 2I	3	3	3	3	3	3	3	3	2b	2b	3	3
7	LGMD 2A	A, 2b	3	2b	2b	3	3	3	3	2b	2b	3	3
8	LGMD 2A	2a	3	1	1	2a	3	3	3	1	1	2b	2b
9	LGMD 2A	2b	3	2b	2b	2a	3	3	3	2b	2b	2a	3
10	LGMD 2A	A, 2b	2b	1	1	2a	A, 3	A, 3	A, 3	0	0	2a	2a
11	LGMD 2A	A, 2b	3	1	2a	2a	3	3	2b	1	2b	3	3
12	LGMD 2B	2a	2a	2b	3	2b	3	3	3	2b	2b	2b	2b
13	LGMD 2B	2a	2a	2b	2b	H, 2a	3	3	3	2b	2b	2b	2b
14	LGMD 2B	2a	1	3	2b	2b	3	3	3	2b	3	3	3
15	LGMD 2B	1	0	2b	2b	2a	2a	2a	2a	0	0	3	3
16	LGMD 2B	1	1	3	2b	1	2a	2a	2a	2b	3	3	3
17	LGMD 2D	2b	2b	2b	3	H	3	3	2b	0	2a	2b	2a
18	LGMD 2D	A, 2b	3	3	3	H	3	2a	2b	0	0	0	0
19	Becker	2b	3	3	3	3	3	2b	2b	0	1	1	3
20	Becker	1	2b	2b	2b	H	1	1	1	0	1	0	3

A Atrophy; *GMa* gluteus maximus; *GMe* gluteus medius; *VL/VIM* vastus intermedio-lateralis; *VM* vastus medialis; *G* Gastrocnemius; *H* hypertrophy; *AM* adductor magnus; *SM* semimembranosus; *BF* biceps femoris; *TA* tibialis anterior; *PL* peroneus longus; *S* Soleus; *Gc* Gastrocnemius; *nd* not done

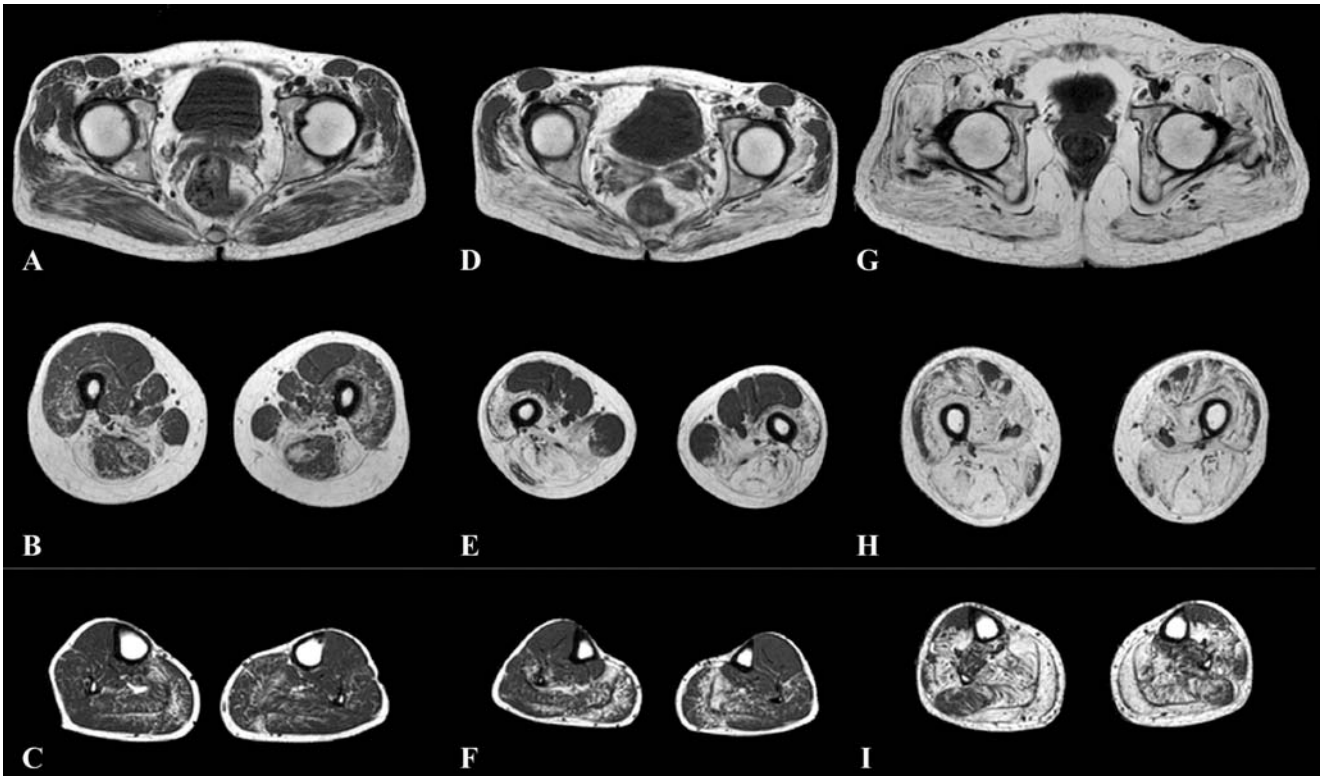

Fig. 2 Muscle MRI of three LGMD2I patients on the pelvic (**A, D, F**), thigh (**B, E, G**) and lower leg (**C, F, H**) level. In a patient with a mild clinical phenotype (**A, B, C**) the most severe changes are seen in the adductor and biceps femoris muscles. In a patient with a moderate phenotype (**D, E, F**) additional severe changes are observed in the semimembranosus and semitendinosus, vastus intermediolateralis and to a lesser degree, in the gluteus maximus muscles. In a patient with a severe clinical phenotype (**G, H, I**) additional muscle groups including in the upper and lower legs displayed severe involvement, too

less affected. However, when involvement of the quadriceps muscle was seen in contrast to LGMD2I the degree of involvement was similar between vastus intermediolateralis muscle and the vastus medialis and rectus femoris muscle (Fig. 3H). Lower legs: all five LGMD2A patients showed a relative selective (moderate to severe) involvement of the medial head of the gastrocnemius muscle and soleus muscle with relative sparing of lateral head of the gastrocnemius muscle. Furthermore, there was diffuse but less severe involvement of the muscles of the anterior lower leg muscles in three patients (Fig. 3C, F, I).

Dysferlinopathy

The pattern of muscular weakness in five patients with dysferlinopathy was less homogeneous than in LGMD2I and LGMD2A patients. Upper limbs: shoulder abduction was weaker than adduction in three patients, but equal in two. Shoulder internal and external rotation strength was equal in all five patients. Elbow flexion was weaker than elbow extension in four patients, whereas one patient had no weakness of elbow flexion or extension. Scapular winging was absent in all patients. Lower limb muscles: were generally much more affected than the upper limb muscles. Hip adduction and abduction was equally affected in four patients, hip flexion was weaker than extension in three and stronger in two patients. Knee flexion was weaker than extension in two, stronger in two and equal in one patient. In contrast to LGMD2I, all patients showed severe weakness of ankle plantarflexion, although two patients had a similar degree or even more affection of ankle dorsiflexion.

MRI findings of patients with dysferlinopathy with a mild, moderate and severe clinical phenotype are illustrated in Fig. 4. Pelvis muscles: all patients had mild to moderate diffuse hyperintense signal changes in the gluteus maximus and medius muscles, which were equal in three patients. In two patients the gluteus maximus muscle showed more severe changes than the gluteus medius muscle. Thigh: all patients had moderate to severe hyperintense signal changes in both the anterior and posterior compartment. However, three patients had more involvement of the posterior compartment

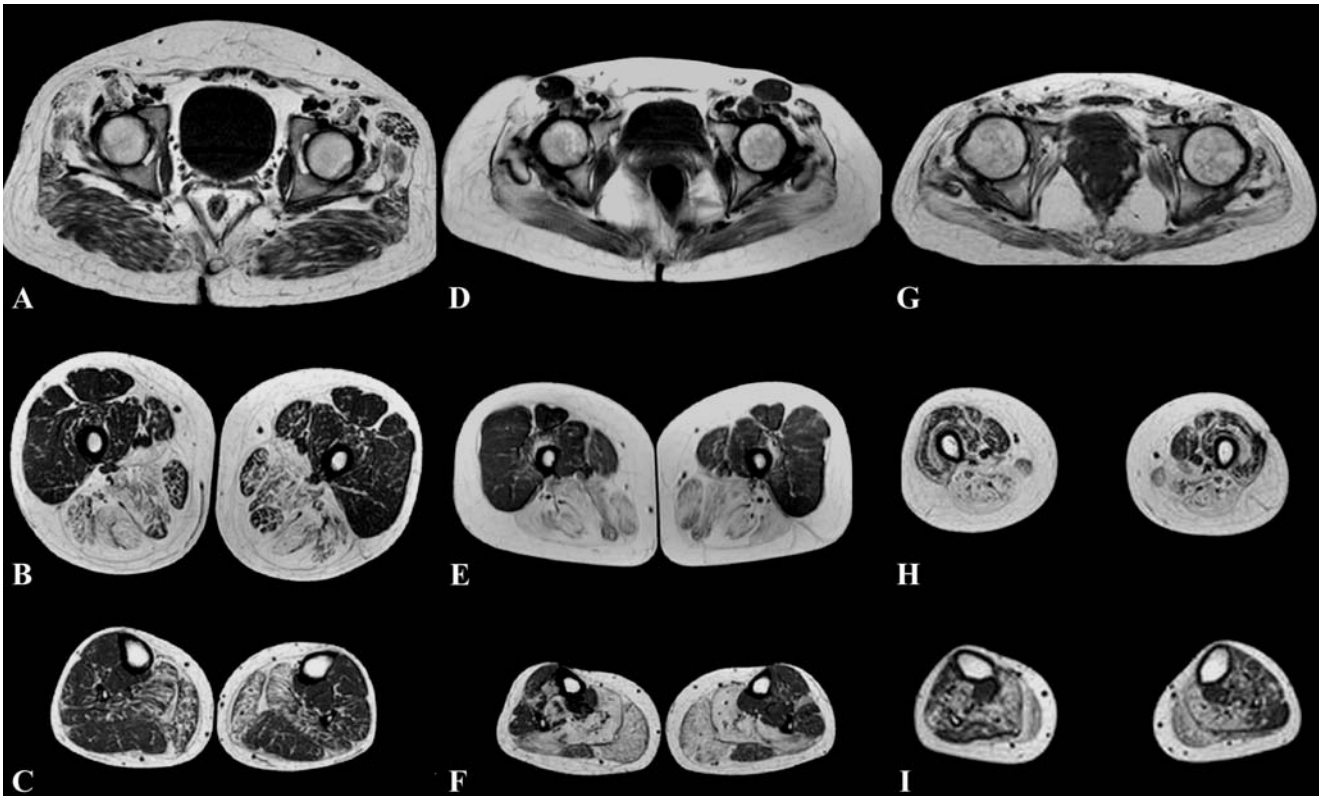

Fig. 3 Muscle MRI of three patients with genetically confirmed primary calpainopathy (LGMD2A) with a mild (**A, B, C**), moderate (**D, E, F**) and severe (**G, H, I**) clinical phenotype. It is noteworthy that, at the pelvic level there is progressive atrophy of the gluteaus maximus muscle (**A, D, F**), which is not seen in LGMD2I and LGMD2B. At the thigh level, similar to LGMD2I, the earliest and most severe changes are observed in the adductor and posterior compartment muscles, whereas in patients with a severe phenotype (**G, H, I**) additional changes are seen in the quadriceps muscle. In contrast to LGMD2I, vastus intermediolateralis and vastus medialis/rectus femoris muscle are involved at the same degree (**H**). In the lower legs, there is a characteristic pattern of relative homogeneous and selective involvement of the medial head of the gastrocnemius and the soleus muscle, which is not seen in other LGMDs

and the adductor muscles (Fig. 4E, H), whereas in two patients the quadriceps muscle was more involved than the hamstrings and adductor muscles (Fig. 4B). Lower legs: all patients showed severe involvement of the gastrocnemius and soleus muscle. In four patients there were additional severe hyperintense signal abnormalities in the anterior lower leg compartment, too.

Dystrophinopathy

In contrast to LGMD2I, both patients with Becker's disease showed weaker hip abduction than adduction and weaker knee extension than flexion. Both patients had calf hypertrophy but no shoulder girdle or upper limb weakness and no scapular winging.

Furthermore, on MRI both showed mild to moderate hyperintense changes in the gluteus medius, whereas the changes in the gluteus maximus were less severe. At the thigh there was marked involvement of the entire quadriceps muscle, while the posterior compartment muscles showed only mild to moderate hyperintense signal changes. In both patients hypertrophy of the sartorius muscle was observed. In the lower legs, a selective severe involvement of both heads of the gastrocnemius muscle with relative sparing of other muscles was observed in both patients (Fig. 5).

Alpha-sarcoglycanopathy

Clinically, the pattern of pelvic girdle muscular involvement in both patients with alpha-sarcoglycanopathy was more similar to dystrophinopathy than to LGMD2I. Both patients showed more weakness of knee extension than flexion and equal involvement of the hip abductors and adductors. However, in contrast to Becker's dystrophy both patients displayed profound weakness of the shoulder girdle muscles.

On MRI, the pattern of muscular involvement of the thigh muscles was similar to Becker's muscular dystrophy with severe involvement of the quadriceps muscle exceeding the affection of the posterior thigh compartment and hypertrophy of the gracilis and sartorius muscle. In the lower legs, however, changes were different from those in dystrophinopathy. Diffuse moderate changes in the soleus and to a lesser degree in the peroneal longus and in the lateral gastrocnemius muscle were observed in one patient. The marked involvement of the gastrocnemius muscle, seen in dystrophinopathy, was not observed in the patients with alpha-sarcoglycanopathy (Fig. 5).

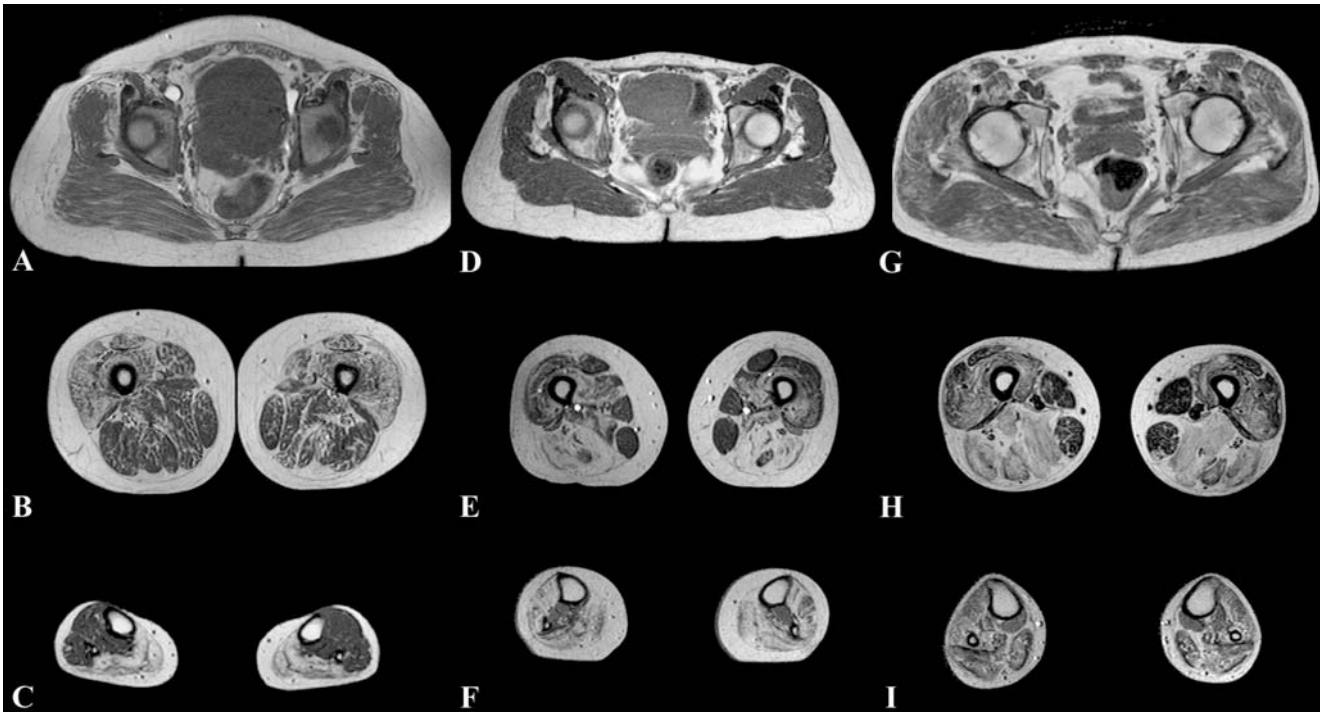

Fig. 4 Muscle MRI in dysferlinopathy in three patients with a mild (**A, B, C**), moderate (**D, E, F**) and severe (**G, H, I**) clinical phenotype. At the pelvic level, there are mild to moderate signal changes in the gluteus minimus muscle in all patients. At the thigh level, there is predominant anterior compartment involvement in some patients (**B**), whereas the posterior compartment muscle exceeds the anterior compartment muscle involvement in others (**E, H**). A similar heterogeneity is observed in the lower legs. Some patients show a relative selective involvement of the gastrocnemius and soleus muscle (**C**), whereas others show marked hyperintense signal abnormalities in the anterior lower leg compartment, too (**F**). In the patient with a severe clinical phenotype, all muscles in the lower leg show a similar pattern of involvement (**I**)

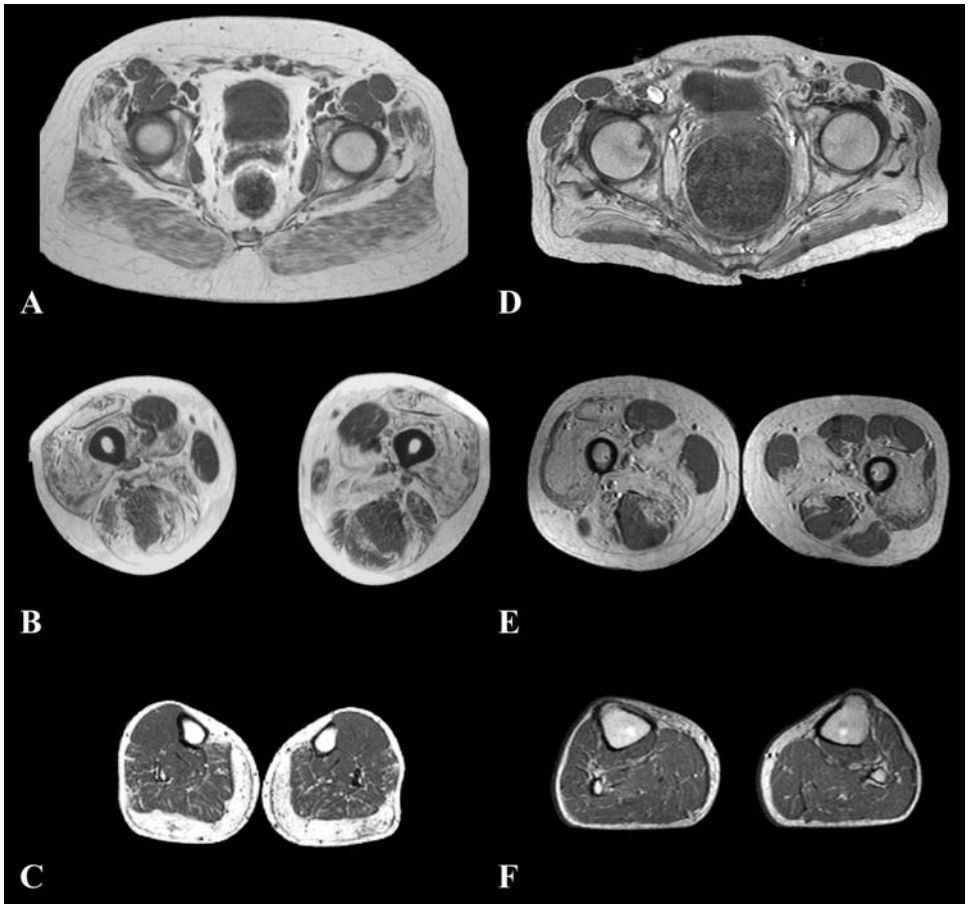

Fig. 5 Muscle MRI of a patient with dystrophinopathy (**A, B, C**) and a patient with alpha-sarcoglycanopathy (**D, E, F**). In contrast to LGMD2I in both dystrophies there is more involvement of the quadriceps muscle than the posterior thigh compartment muscles (**B, E**). However, in the lower limbs in dystrophinopathy Becker type the most severe changes are observed in both heads of the gastrocnemius muscle (**C**), which is not seen in alpha-sarcoglycanopathy (**F**)

Discussion

In the present study we performed a systematic clinical and muscular MRI assessment in 20 patients with genetically confirmed diagnosis of LGMD or dystrophinopathy. Our detailed clinical and MRI analysis showed a distinct and consistent pattern of muscular involvement in LGMD2I. Predominant weakness of shoulder adduction and internal rotation, elbow flexion, hip flexion and adduction, knee flexion and ankle dorsiflexion was observed that clearly exceeded the degree of weakness in the shoulder abductors, elbow extensors, hip extensors and abductors, knee extensors and ankle plantarflexors. This pattern seems to be independent of the individual disease duration and the level of clinical severity in our series of LGMD2I patients. The pattern of muscular weakness was also mirrored in our muscle MRI analysis. Marked hyperintense signal changes on T1 weighted images were seen in the adductor and posterior thigh muscles that clearly exceeded the changes in the abductor and anterior thigh muscles. Hypertrophy of the gracilis and sartorius muscle seems to be a frequent finding. Furthermore, the degree of signal abnormalities in affected muscles mirrored the degree of muscle weakness in individual patients. The presented MRI data in patients with different clinical disease severity point towards a specific temporal pattern of muscular involvement in LGMD2I. At the pelvic level, the gluteus maximus is earlier and more severely involved than the gluteus medius. At the thigh level the earliest and most severe changes are seen in the biceps femoris and internal adductor muscles. With further disease progression degenerative changes are seen in the remaining hamstring muscles and to a lesser degree in the vastus intermedius and lateralis muscles. Involvement of the vastus medialis and rectus femoris was only observed in the patient with advanced disease. In the lower legs diffuse changes in the medial head of the gastrocnemius and the soleus muscle are observed early in the disease, while involvement of the anterior compartment muscles was only observed in later stages of the disease.

In the next step, we compared the clinical and MRI pattern of muscular involvement in LGMD2I with other genetically confirmed LGMDs and Becker's muscular dystrophy. Our findings showed a clear overlap between LGMD2I and LGMD2A. Both disease entities showed an identical clinical pattern of muscular weakness, a pat-

tern known from LGMD2A (Fardeau et al. 1996; Pollitt et al. 2001). It is noteworthy, however, that calpainopathy differs clinically from LGMD2I in some important features: the rare occurrence of generalised or calf hypertrophy (seen in two thirds of LGMD2I patients) and the absence of cardiac involvement (occurring in about 30 % of LGMD2I patients) (Mercuri et al. 2003; Poppe et al. 2003). Furthermore, on MRI there are distinctive features that allow a differentiation between both disease entities. In contrast to LGMD2I, in LGMD2A a selective involvement of the medial gastrocnemius and soleus muscle were observed (Fig. 3C, F, I). In addition, in LGMD2I affection of the vastus intermediolateralis muscle preceded the involvement of the vastus medialis and rectus femoris muscles, whereas in all our LGMD2A patients both muscle groups showed a similar degree of involvement. Interestingly, the pattern of predominant posterior thigh involvement and the relatively selective involvement of the medial head of the gastrocnemius muscle and soleus muscle in the lower legs was observed in all LGMD2A patients and seems to be highly characteristic for primary calpainopathies. This may have important diagnostic implications, because about 20 % of patients with mutations in the calpain-3 gene lose the Ca(++)-dependent autocatalytic activity of calpain-3 and show no protein expression abnormality on western blotting (Fanin et al. 2003). In keeping with this hypothesis, we identified a homozygous mutation in the autocatalytic region in patient 11 (with normal calpain-3 expression on western blotting), in whom we initiated genetic testing after the results of the muscular MRI (Fig. 3D, E, F).

Prominent signal changes in the posterior thigh muscles exceeding those in the anterior muscles have also been reported in muscular imaging studies on dysferlinopathies (Cupler et al. 1998; Linssen et al. 1997; Mahjneh et al. 2001; Miyoshi et al. 1986). However, in contrast to LGMD2I and LGMD2A, the pattern of muscular involvement in our dysferlinopathies was more variable. Various initial clinical presentations have been reported in dysferlinopathies ranging from distal posterior weakness (Miyoshi et al. 1986), distal anterior weakness (Illa et al. 2001) to proximal lower limb weakness (Bashir et al. 1998; Mahjneh et al. 2001; Weiler et al. 1999). Our data imply that predominant muscle pathology might either be in the anterior or in the posterior thigh compartment in patients with LGMD2B. Clinical examination may distinguish dysferlinopathies from LGMD2I patients. In dysferlinopathies the calf muscles are often the earliest and most severely affected muscles leading to pronounced weakness of plantarflexion. Arm and shoulder girdle muscles are only affected in advanced stages of the disease and involvement is always milder than in the lower limbs. Scapular winging and cardiac involvement are absent in dysferlinopathies (Linssen et al. 1997; Miyoshi et al. 1986; Weiler et al. 1999). Recently published studies emphasised a clinical overlap between LGMD2I and the group of dystrophinopathies (Bonnemann and Finkel 2002; Mercuri et al. 2003; Poppe et al. 2003). However and in clear contrast to LGMD2I, our patients with Becker's disease showed weaker hip abduction than adduction and weaker knee extension than flexion. In keeping with this clinical observation, we observed pronounced signal changes in the anterior rather than the posterior thigh muscles in all patients with muscular dystrophy type Becker and alpha-sarcoglycanopathy on MRI. In accordance with our results, a predominant involvement of the anterior thigh compartment has been observed in dystrophinopathy and LGMD2D (Eymard et al. 1997; Lamminen 1990; Liu et al. 1993; Lodi et al. 1997). Thus, the relation between knee extensor and flexor involvement seems to be useful to distinguish muscular dystrophy type Becker and LGMD2D from LGMD2I clinically and on muscular MRI. Furthermore, the milder involvement of the upper limb muscles in Becker's dystrophy compared with LGMD2I patients is helpful in distinguishing both disease entities clinically. Finally, alpha-sarcoglycanopathy can be differentiated from muscular dystrophy type Becker by the greater extent of upper limb involvement (Eymard et al. 1997) and by the different pattern in the lower limbs on muscular MRI (Lodi et al. 1997) (Fig. 5).

In conclusion, our results indicate that muscular MRI is a powerful tool with which to differentiate individual forms of LGMDs. Since LGMD2I due to the common Leu276Ile mutation is one of the most common mutations leading to muscular dystrophies in adult patients in Europe (Walter et al. 2004), the recognition of this specific muscular phenotype may enable direct genetic testing. Furthermore, in primary calpainopathies a characteristic pattern with selective involvement of the medial gastrocnemius and soleus muscle was observed on muscle MRI. This may be particularly helpful to identify LGMD2A patients who do not show abnormalities on calpain-3 Western blotting (Fanin et al. 2003). Beyond the diagnostic implications, our MRI findings provide evidence that different disease groups show characteristic patterns of muscular involvement. While mutations in genes encoding proteins of the DAG (dystrophin, alpha-sarcoglycan) predominantly affect the anterior thigh muscles, proteins with enzyme function (calpain-3, FKRP) predominantly involve the posterior thigh muscles.

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