Atypical Phenotypes in Patients With Facioscapulohumeral Muscular Dystrophy 4q35 Deletion

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Background: Facioscapulohumeral muscular dystrophy (FSHD) is associated with a deletion on chromosome 4q35. Recent studies have shown that this deletion is found in patients with other phenotypes in addition to those with the classic Landouzy-Dejerine FSHD phenotype.

Objective: To examine patients with atypical phenotypes and an FSHD deletion on chromosome 4q35.

Design: Clinical characterization and genotype-phenotype correlation.

Setting: University hospital.

Patients: Forty-one symptomatic subjects with deletions on chromosome 4q35.

Results: We found 6 patients with atypical FSHD. Three (from a single family with FSHD) had additional symptoms of chronic progressive external ophthalmoplegia (4q35 EcoRI/BlnI fragment size, 20 kilobase [kb]), and 3 patients (1 with sporadic disease and 2 from a single family) had facial-sparing scapulohumeral dystrophy (4q35 EcoRI/BlnI fragment size, 30 and 34 kb, respectively).

Conclusions: The clinical presentations in patients with FSHD-associated short fragments on chromosome 4q35 are not restricted to the classic FSHD form, but constitute a variety of clinical manifestations. There seems to be no clear correlation between the atypical subtype and the DNA fragment size due to the deletion.

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Facioscapulohumeral muscular dystrophy (FSHD) is one of the most common forms of familial muscular dystrophy, with an estimated incidence of 1:20000.¹ The classic description of Landouzy and Dejerine² from 1884 still constitutes the fundamental FSHD clinical diagnostic criteria.³

The onset of symptoms in FSHD varies from infancy to middle age. The degree of involvement ranges from minimal facial weakness to severe generalized palsies. Facioscapulohumeral muscular dystrophy initially affects the facial and scapular muscles and upper-arm and foot dorsiflexion, and later affects the proximal hip muscles. The course usually progresses slowly; approximately 20% of patients eventually become wheelchair dependent.¹

Facioscapulohumeral muscular dystrophy is an autosomal dominant inherited disorder and is linked in 95% of cases to chromosome 4q35. A deletion of multiple copies of a tandem repeat consisting of 3.3-kilobase (kb) units (D4Z4) is associated with the disease. Restriction enzyme cleavage with EcoRI alone and EcoRI/BlnI allows the distinction of the 4q35 locus from a homologous locus on chromosome 10q26 in most individuals. The EcoRI/BlnI fragments in the range of 10 to 35 kb on chromosome 4q35 are assumed to be disease associated and can be detected by probe p13E-11 with a test sensitivity of 95% and a specificity approaching 100% at the 34-kb level.⁴ Sporadic cases can occur and are presumably the result of new mutations.⁵

Recent studies have shown that the 4q35 deletion is found in patients with the classic form of FSHD and in patients with phenotypes such as the facial-sparing form of FSHD (SHD),⁶ limb-girdle muscular dystrophy,⁷ distal myopathy,⁸ or asymmetric brachial weakness.⁷ The present study describes 6 patients from 3 unrelated families with atypical FSHD and partially undescribed phenotypes.

METHODS

The 6 patients described in this report were selected from 41 consecutive symptomatic patients in whom the FSHD deletion could be demonstrated. We extracted DNA from the...
peripheral blood leukocytes by means of standard procedures. For detection of 4q35 deletions, DNA was cleaved with EcoRI and EcoRI/BlnI and electrophoretically separated on 0.7% agarose gels in 1× TAE (Tris–acetic acid–EDTA) buffer for 40 hours at 1.2 V/cm. DNA cut with HindIII or XhoI and marker 19 (MBI Fermentas GmbH, St Leon–Roth, Germany) were used as size markers. The DNA was transferred to membranes (Hybond N+; Amersham Biosciences, Freiburg, Germany) and hybridized with radioactively labeled probe p13E-11 (D4F104S1). Bands were then visualized by means of autoradiography. To rule out a deletion on chromosome 4q35, the BglII/BlnI dosage test was performed as described previously. Of 41 patients with FSHD with typical deletions, we identified 6 (2 from 1 family, 3 from 1 family, and 1 sporadic case) with atypical (no Landouzy-Dejerine phenotype) clinical features (Table). These atypical phenotypes could be classified into subgroups.

### FSHD WITH CHRONIC PROGRESSIVE EXTERNAL OPHTHALMOPLEGIA

Three patients from a single family (F1) showed the typical FSHD phenotype associated with additional chronic progressive external ophthalmoplegia (CEPO).

**Patient F1-1**

A 50-year-old man was referred for bilateral arm and shoulder girdle weakness since 25 years of age and slowly progressive ptosis without double vision throughout his lifetime. The family history was remarkable for leg weakness in his grandfather. His parents and grandparents were dead, and his only relatives were 2 children. In both children, ptosis and impaired ocular movements were observed (patients F1-2 and F1-3). The neurological examination revealed facial weakness, bilateral ptosis, oculomotor impairment (restricted upward gaze with the right eyeball, deviation to nasal, and minimal restricted right eyeball abduction), symmetric-predominant proximal arm and shoulder girdle paresis and atrophy, bilateral scapular winging, lumbar hyperlordosis, prominent foot drop, and moderate hip flexor paresis (Figure 1). The serum creatine kinase (CK) level was elevated (320 U/L; reference range, <80 U/L). Cranial magnetic resonance imaging findings were normal. Serum lactate level was within the reference range at rest and upon bicycle exercise. Electromyography findings showed reduced amplitude and duration of motor unit action potentials (MUAPs). Results of a muscle biopsy demonstrated prominent myopathic changes without ragged red fibers and histopathological features of other neuromuscular diseases. There were no singular or multiple deletions of mitochondrial DNA. The EcoRI restriction fragment of 23 kb was reduced to 20 kb by additional cleavage with BlnI. The BglII/BlnI dosage

### RESULTS

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<table>
<thead>
<tr>
<th>Subtype, Patient No.</th>
<th>Sex/Age, y</th>
<th>EcoRI/BlnI Fragment Length, kb</th>
<th>Typical Presentations</th>
<th>Atypical Presentations</th>
</tr>
</thead>
<tbody>
<tr>
<td>FSHD with CPEO</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>F1-1</td>
<td>M/50</td>
<td>20</td>
<td>FSHD</td>
<td>CPEO</td>
</tr>
<tr>
<td>F1-2</td>
<td>M/15</td>
<td>20</td>
<td>Winged scapula; lumbar hyperlordosis</td>
<td>CPEO</td>
</tr>
<tr>
<td>F1-3</td>
<td>F/15</td>
<td>20</td>
<td>Winged scapula; lumbar hyperlordosis</td>
<td>CPEO</td>
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<tr>
<td>SHD</td>
<td></td>
<td></td>
<td>SHD</td>
<td></td>
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<tr>
<td>F2-1</td>
<td>F/61</td>
<td>34</td>
<td>SHD</td>
<td>No facies myopathica</td>
</tr>
<tr>
<td>F2-2</td>
<td>F/60</td>
<td>34</td>
<td>SHD</td>
<td>No facies myopathica; severe myalgia</td>
</tr>
<tr>
<td>S1</td>
<td>M/29</td>
<td>30</td>
<td>SHD</td>
<td>No facies myopathica; severe myalgia</td>
</tr>
</tbody>
</table>

Abbreviations: CPEO, chronic progressive external ophthalmoplegia; F1, family 1; F2, family 2; FSHD, facioscapulohumeral muscular dystrophy; kb, kilobase; S1, sporadic case; SHD, facial-sparing scapulohumeral dystrophy.
test revealed 2 chromosome 4q35–type and 2 chromosome 10q26-type fragments.

Patient F1-2

The 15-year-old boy was delivered by cesarean section. Since infancy, he had noticed progressive bilateral ptosis. Motor development was delayed (reduced crawling, walking at 18 months of age). At 7 years of age, the patient underwent surgical correction of prominent strabismus. The neurological examination revealed bilateral ptosis, divergent strabismus, asymmetrically restricted eye movements with up gaze worse in the right than the left eye and down gaze worse in the left than in the right eye, slightly limited horizontal movement of both eyes, no facial weakness, minimal bilateral scapular winging, and lumbar hyperlordosis (Figure 1 and Figure 2). The serum CK level was within the reference range. Electromyography findings showed reduced amplitude and duration of MUAPs. Results of bicycle exercise testing were normal. A muscle biopsy specimen demonstrated minimal myopathic changes without ragged red fibers. Molecular analysis revealed an EcoRI/BlnI restriction fragment, as could be seen in his father.

Patient F1-3

The 15-year-old girl was delivered by cesarean section. Since infancy, she had noticed progressive bilateral ptosis. Her motor development was delayed (very reduced crawling, walking at 18 months of age). At 7 years of age, she underwent surgical correction of a prominent strabismus. At 2 and 7 years of age, ptosis was corrected. The neurological examination revealed bilateral ptosis, divergent strabismus, downward and horizontal bilaterally restricted eye movements, left eye deviation without conjugation, no facial weakness, minimal bilateral scapular winging, and lumbar hyperlordosis. The serum CK level was within the reference range. Electromyography findings showed reduced amplitude and duration of MUAPs. Muscle biopsy was not performed. Results of molecular analysis revealed an EcoRI/BlnI restriction fragment, as could be seen in her father.

FACIAL-SPARING FORM

Three patients (2 from family 2 [F2]) had SHD with otherwise typical FSHD features. One patient had only scapulo-humeral dystrophy, whereas 2 had SHD and additional prominent myalgia.

Patient F2-1

This 61-year-old woman was referred for symptoms of progressive limb muscle weakness. At 40 years of age, she first noticed difficulties in climbing stairs and slowly progressive leg weakness. Her mother exhibited different thickness of the legs, and her sister had muscle pain. The mother of the patient was dead, and no other relatives were available. She had no facial weakness, but atrophy of the dorsal trunk muscles and bilateral infraspinatus and supraspinatus muscles, slight muscular atrophy of the right extremities, scapular winging that was worse on the right than on the left, bilateral paresis of arm retroversion, foot drop, minimal proximal leg and pelvic girdle weakness, striking Gothic palate, thoracic scoliosis, and lumbar hyperlordosis were seen. The serum CK level was elevated (360 U/L). Results of a muscle biopsy demonstrated moderate myopathic changes. The molecular genetic test revealed an EcoRI/BlnI restriction fragment of 34 kb. The BglII/BlnI dosage test revealed 2 chromosome 4q35– and 2 chromosome 10q26-type copies.

Patient F2-2

The 60-year-old sister of patient F2-1 was referred for chronic muscle pain. Throughout her life, the patient had noticed bilateral, nearly permanent pains in the shoulder girdle and upper arm muscles without joint problems. The pain was described as a continuous ache without exacerbation on exercise; however, spontaneous irregular worsening was described as sharp and stabbing pain. Results of the rheumatological and orthopedic investigations, including labor tests and radiography of shoulder and elbow joints, were normal. The neurological examination revealed no facial weakness, but revealed moderate calf atrophy that was worse on the right than on the left, minimal hip flexor paresis, thoracic hyperkyphosis, and scoliosis. Tendon reflexes were normal. Results of the sensory examination were unremarkable. The serum CK level was elevated (390 U/L). Electromyography findings showed reduced amplitude and duration of MUAPs. A muscle biopsy was not performed. An EcoRI/BlnI fragment of 34 kb could be seen in this patient, as in patient F2-1.

Sporadic Case

A 29-year-old man was referred for chronic generalized muscle pain since 19 years of age. Pain was described as a continuous diffuse aching in all muscle groups, including truncal musculature, with no worsening on exercises. The patient had no joint problems. Rheumatological investigation, including labor tests and spine radiography, revealed no rheumatological disease. There was no
family history of neuromuscular disease and no local muscle weakness. The neurological examination revealed a well-muscled man with no facial weakness, minimal scapular winging that was worse on the right than on the left, minimal right pectoralis major atrophy, and a distinct right quadriceps femoris atrophy. Tendon reflexes and results of sensory examinations were normal. The serum CK level was elevated (387 U/L). Electromyography findings showed reduced amplitude and duration of MUAPs. Results of a muscle biopsy demonstrated moderate myopathic changes. Molecular genetic examination demonstrated a 30-kb EcoRI/BlnI fragment. The BglII/BlnI dosage test revealed 3 chromosome 4q35-type and 1 chromosome 10q26-type fragments.

Our study findings are consistent with those of recent publications, which show that not all patients with the FSHD 4q35 deletion present with the classic FSHD phenotype described by Landouzy and Dejerine. Six (15%) of our 41 patients or 3 (11%) of 28 unrelated families with FSHD-typical genetic defects on chromosome 4q35 did not fulfill the clinical criteria of the European Neuromuscular Centre for Landouzy-Dejerine FSHD. However, the underlying gene defect for FSHD has not been identified. Molecular genetic studies test only for an association of a deletion of copies of tandem repeats on chromosome 4q35 with the disease. The test is highly specific, but false-positive or false-negative results cannot be excluded. In contrast to previous studies about atypical FSHD, we performed the BglII/BlnI dosage test, which helps identify translocations between 4q35 and 10q26. The BglII/BlnI dosage test revealed 2 chromosome 4q35-type and 2 chromosome 10q26-type copies in our 2 families. These data support an origin of the 20-kb fragment size due to the deletion. Consistent with a previous study, there seems to be no clear correlation between the atypical subtype and the fragment size due to the deletion.

The SHD (in both F2 patients and the patient with sporadic disease) in genetically typical FSHD was already described by Jardine et al and seems to be the most common atypical presentation of FSHD. The term facial-sparing SHD should only be used for sporadic cases and cases in families without facial muscle weakness in all family members, as it could be shown in our F2 patients and in our patient with sporadic disease. It is well known that in some families with typical FSHD, a proportion of clinically affected members may not have facial weakness. According to the FSHD diagnostic criteria of the European Neuromuscular Centre, our patients did not have typical FSHD because facial weakness should be present in more than 50% of the affected family members. Our patient F2-2 with SHD and the patient with sporadic disease reported severe diffuse muscle pain as the most prominent disabling symptom of their condition. Subjectively, these patients had noticed no muscle weakness at all. In contrast, patient F2-1 remembered no muscle pain, whereas this was the only symptom of his sister (patient F2-2). Although moderate shoulder girdle pain is not rare in patients with FSHD, clinical studies of typical FSHD rarely report muscle pain as a significant feature or as the most disabling aspect of the condition.

All 3 F1 patients initially presented with progressive ptosis and ocular movement disorder. Years later, the classic FSHD distribution of muscle weakness developed in patient F1-1 (the father of patients F1-2 and F1-3), in addition to the ocular symptoms. Other possible neuromuscular disorders with extraocular muscle involvement reviewed by Jones and North were clinically, electrophysiologically, and histopathologically excluded. In particular the paternal inheritance, the absence of ragged red fibers and other histopathological changes in a muscle biopsy specimen, a normal result of bicycle exercise testing, and the absence of single or multiple deletions of mitochondrial DNA excluded the diagnosis of a coincidental CPEO of mitochondrial origin. However, the possibility of another coincidental cause of CPEO cannot entirely be excluded. The classic FSHD distribution of the muscle weakness in our patients, particularly prominent scapular winging, and lumbar hyperlordosis were never observed in patients with CPEO. A recent study has shown that FSHD occurs only if the deletion is associated with 1 of 2 polymorphisms distal to the D4Z4 repeats. It is, however, unlikely that the nonpathogenic polymorphism is relevant in family 1 because patient F1-1 had all of the classic clinical features of the Landouzy-Dejerine FSHD in addition to the ocular symptoms. In addition, both children already had minimal scapular winging and lumbar hyperlordosis, whereas more prominent FSHD symptoms developed in the father only at 25 to 30 years of age.

It is conceivable that the diagnosis of FSHD is often missed in those patients who do not initially exhibit the typical leading symptoms of the facioscapulohumeral muscular weakness. In none of our patients, except patient F2-1, was FSHD primarily suspected, because clinical presentations in all these cases were extremely different from the FSHD diagnostic criteria. Consistent with a previous study, there seems to be no clear correlation between the atypical subtype and the fragment size due to the deletion.

On the basis of our experience (Table) and those of previous studies, the following atypical variants of clinical presentations (atypical phenotypes) can be distinguished in patients with the FSHD genotype:

1. SHD or facial-sparing SHD with or without myalgia (Felice et al, Felice and Moore, Jardine et al, and the present study)
2. FSHD with CPEO symptoms (present study)
3. Limb-girdle muscular dystrophy syndrome
4. Distal myopathy
5. Asymmetric brachial weakness

Because of the extreme variety of clinical phenotypes in patients with an FSHD genotype, an atypical form of FSHD should be considered in patients with obscure and unclassified myopathies.
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